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The Journal of Allergy

VOL. III JANUARY, 1932 NO. 2

Original Articles

THE PERENNIAL TREATMENT OF SEASONAL HAY FEVER*

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NEW YORK, N. Y.

IN THE April, 1927, issue of the *Journal of Immunology*, I presented "A New Plan for Applying the Specific Treatment of Pollen Hay Fever (Perennial Treatment)."

Some years have elapsed, and this type of treatment has had considerable trial, so that we are now in a better position to judge its value.

In pollen hay fever, we make a diagnosis, qualitatively as to the causal pollen factor and quantitatively as to the degree of sensitivity.

The pollen extracts used are prepared with Coca's alkaline extracting fluid, and are standardized by their nitrogen content.

We determine the degree of sensitivity by the reaction obtained with various standardized solutions, and classify the patients, according to Cooke, as follows:

Class A —marked reaction to 0.0001 mg. N. per c.c.
Class B —marked reaction to 0.001 mg. N. per c.c.
Class C —marked reaction to 0.01 mg. N. per c.c.
Class D —marked reaction to 0.1 mg. N. per c.c.
Class AB—marked reaction to 0.0005 mg. N. per c.c.
Class BC—marked reaction to 0.005 mg. N. per c.c.
Class CD—marked reaction to 0.05 mg. N. per c.c.

The injections, amount, interval and maximum dosage reached, depend upon the classification. The more sensitive the individual, the less is the amount of the extract necessary to protect him.

Treatment is either preseasonal or seasonal. Under the former, the usual method now employed, treatment is begun two or three months prior to the date of expected onset, injections being given at

*Read before the Ninth Annual Meeting of the Association for the Study of Allergy, Philadelphia, June 8, 1931.

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from five- to seven-day intervals to reach the maximum dosage in the class just before the hay fever season begins. Under the latter, an effort is made to bring rapidly the patient's immunity by injections given daily or every other day. Injections are continued throughout the season.

At the present time, treatment stops with the termination of the pollen season, to be resumed again the following year. Whatever tolerance has been built up in the patient is lost to a degree, that has not heretofore been determined, making it necessary to start the treatment each year as though the case were a new one.

We have now for ten years been treating some of these pollen cases throughout the year, and our greater experience fully bears out the conclusion heretofore reached, to wit, that this method offers us a good means of obtaining better results than with the seasonal treatment and better hopes for permanent results.

Two factors of prime importance had to be reckoned with in undertaking this treatment: first, whether the interval between injections could be extended long enough; second, whether the clinical protection obtained was as good as that obtained by the previous method.

The first question was answered by experimentally increasing the intervals first to ten days, then two weeks, three weeks, four weeks or longer—and watching for constitutional reactions demonstrating a lack of tolerance. We are now in a position to state that constitutional reactions appear less often than they do under preseasonal treatment.

The main difficulty presented in the perennial treatment was the possibility of a constitutional reaction upon changing from an old, somewhat deteriorated extract to a new and therefore more active one.

This theoretical difficulty has been overcome in several ways:

First, the improved method of preparing the extracts has considerably lessened the degree of deterioration. Second, the precaution is taken to keep the extracts at a low temperature of 40°. Third, the extract is bottled into small vials, all the dilutions for the year's use being made up at one time. Fourth, in changing from an old to a new extract, we change gradually, using a mixture of the new extract. I make the change by adding two-thirds of the dose of the old extract to one-third dose of the new extract. The next dose, three or four weeks later, two-thirds of the new and one-third of the old. The next dose, the new extract only.

One may also, if time is a factor, rapidly change from the old to the new extract by giving injections weekly, with mixtures of the old and new extracts to change rapidly to the new.

I have made many tracings during the past few years, comparing the old and the new extracts, using sites other than the injected areas

for comparison. These tracings indicate very little if any deteoriations in the extracts in a year.

Constitutional Reactions.—In the experience of workers in this field, constitutional reactions varying from mild hay fever to severe urticaria and asthma, average about one in every 200 injections. There are certain individuals prone to constitutional reactions. Such reactions are due to:

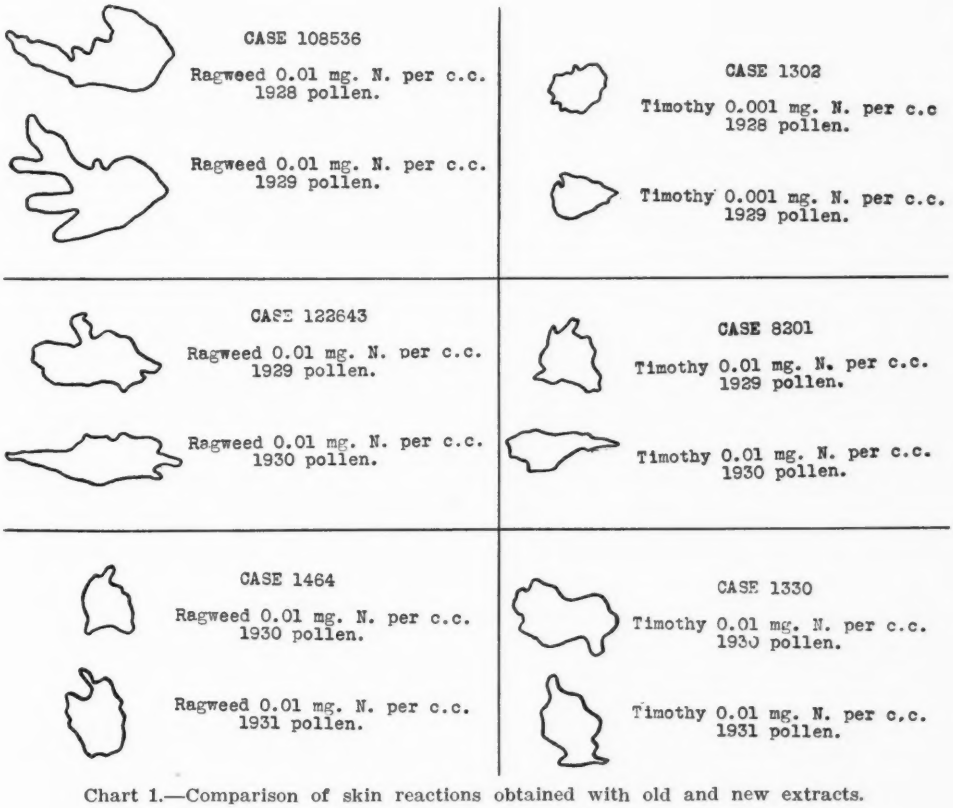
CASE 108536
Ragweed 0.01 mg. N. per c.c. 1928 pollen.
Ragweed 0.01 mg. N. per c.c. 1929 pollen.
CASE 1302
Timothy 0.001 mg. N. per c.c 1928 pollen.
Timothy 0.001 mg. N. per c.c. 1929 pollen.
CASE 123643
Ragweed 0.01 mg. N. per c.c. 1929 pollen.
Ragweed 0.01 mg. N. per c.c. 1930 pollen.
CASE 8301
Timothy 0.01 mg. N. per c.c. 1929 pollen.
Timothy 0.01 mg. N. per c.c. 1930 pollen.
CASE 1464
Ragweed 0.01 mg. N. per c.c. 1930 pollen.
Ragweed 0.01 mg. N. per c.c. 1931 pollen.
CASE 1330
Timothy 0.01 mg. N. per c.c. 1930 pollen.
Timothy 0.01 mg. N. per c.c. 1931 pollen.

Chart 1.—Comparison of skin reactions obtained with old and new extracts.

1. Injection into a vein, which can be obviated by withdrawing the syringe from the needle to see whether bleeding occurs.

2. Overdose. It is always better to use larger amounts of weaker dilutions, e.g., to give a dose of 0.02, it is better to use 0.4 of 0.05 solution than 0.2 of 0.1 solution. Also to use fresh bottles of extract instead of completely using up the old.

3. We have also proved that the dose, where a greater number of constitutional reactions occur, is in going from 0.01 to 0.015. We have therefore always used 0.0125 as a step-up dose.

4. Maximum dosage. We have found that some people can only tolerate a certain dose, the slightest increase producing a constitutional reaction.

TABLE I

POLLEN CASES TREATED PERENNIALLY

NO.	CASE	AGE	YEARS DURATION HAY FEVER	TYPE AND CLASS	PERENNIAL STARTED	MAXIMUM DOSE IN 1930	INTERVAL	CONSTITUTIONAL REACTION	RESULTS IMPROVEMENT
1	108536	50	10	Late B	1924	Ragweed 0.06	Monthly	None	90-95%
2	122643	47	12	Late C	1925	Ragweed 0.1	Monthly	None	95%
3	J. G.	59	10	Late C	1924	Ragweed 0.1	3-4 wk.	None	75-85%
4	B. G.	39	9	Early B Late C	1924	Timothy 0.025 Ragweed 0.1	4 wk.	None	95% both
5	122746	34	10	Late C	1924	Ragweed 0.1	Monthly	None	95%
6	123205	61	21	Late C	1925	Ragweed 0.1	Monthly	None	80%
7	106356	37	11	Late C	1925	Ragweed 0.1	Monthly	None	90%
8	108945	54	8	Late C	1926	Ragweed 0.1	Monthly	None	95%
9	109235	36	24	Late BC	1926	Ragweed 0.1	Monthly	None	95%
10	S. M.	47	12	Late BC	1926	Ragweed 0.08	3-4 wk.	1/14/29 to Ragweed 0.09 9/ 8/30 to Ragweed 0.1	90%
11	133753	41	11	Late C	1926	Ragweed 0.07	3-4 wk.	None	90%
12	L. A.	33	14	Early C Late BC	1926 1926	Timothy 0.05 Ragweed 0.035	3-4 wk.	10/17/28 to Ragweed 0.06 3/22/29 to Ragweed 0.035 4/12/29 to Ragweed 0.04	Early 95% Late 75%
13	32	52	42	Early BC	1920	Timothy 0.035	Monthly	3/27/25 to Timothy 0.025	95-98%
14	200	40	18	Early C	1922	Timothy 0.13	Monthly	11/ 9/27 to Timothy 0.15 7/17/28 to Timothy 0.2	95%
15	269	18	9	Early BC Late C	1924	Timothy 0.045 Ragweed 0.1	3 wk.	None	90%
16	95	49	20	Early B Late C	1921	Timothy 0.015 Ragweed 0.1	2-3 wk.	7/12/21 to Timothy 0.015 from Timothy 0.009	Early 80% Late 90%
17	303	30	9	Late C	1925	Ragweed 0.1	Monthly	None	100%
18	714	40	14	Late C	1925	Ragweed 0.1	3-4 wk.	None	90%
19	719	32	18	Late C	1925	Ragweed 0.1	4 wk.	None	85%
20	847	44	8	Late C	1925	Ragweed 0.1	3-4 wk.	None	95%
21	833	46	8	Early B Late C	1926	Timothy 0.04 Ragweed 0.1	4 wk.	None	95%
22	877	45	9	Late C	1926	Ragweed 0.1	3 wk.	None	90%

TABLE I—CONT'D

NO.	CASE	AGE	YEARS DURATION HAY FEVER	TYPE AND CLASS	PERENNIAL STARTED	MAXIMUM DOSE IN 1930	INTERVAL	CONSTITUTIONAL REACTION	RESULTS IMPROVEMENT
23	826	30	12	Late C	1926	Ragweed 0.1	4-5 wk.	None	95%
24	1302	43	15	Early BC	1926	Timothy 0.04 Plantain 0.08	Monthly	None	90%
25	993	21	9	Early BC	1927	Timothy 0.05	3 wk.	None	95%
26	1036	29	8	Late C	1927	Ragweed 0.02	2 wk.	3/17/30 to Ragweed 0.01 from Ragweed 0.007 4/26/30 to Ragweed 0.025	80%
27	1037	25	8	Late C	1927	Ragweed 0.1	3 wk.	8/20/28 to Ragweed 0.075 9/14/28 to Ragweed 0.075	80%
28	1049	42	7	Late C	1927	Ragweed 0.1	4 wk.	None	100%
29	1052	40	12	Late B	1927	Ragweed 0.035	2 wk.	None	90%
30	828	43	15	Late C	1927	Ragweed 0.1	3-4 wk.	None	85%
31	883	38	9	Early C	1927	Timothy 0.13	3 wk.	None	100%
32	1107	40	12	Early AB Late C	1927	Timothy 0.008 Ragweed 0.1	3 wk.	6/ 8/28 to Timothy 0.002 7/ 2/29 to Timothy 0.006	Early 75% Late 90%
33	1109	46	10	Late C	1928	Ragweed 0.1	3-4 wk.	None	95%
34	1153	51	9	Late B	1928	Ragweed 0.025	17 days	3/22/29 to Ragweed 0.006	80%
35	1136	39	5	Early C Late C	1928	Timothy 0.1 Ragweed 0.1	3-4 wk.	None	90%
36	713	29	5	Late B	1929	Ragweed 0.02	2 wk.	3/24/30 to Ragweed 0.04 4/20/30 to Ragweed 0.025 8/25/30 to Ragweed 0.025	80%
37	1292	26	10	Early B Late C	1929	Timothy 0.025 Ragweed 0.1	3-4 wk.	None	Early 90% Late 80%
38	1319	38	11	Late C	1929	Ragweed 0.1	3 wk.	None	100%
39	1315	37	30	Late C	1929	Ragweed 0.1	3 wk.	None	95%
40	1341	33	9	Late C	1929	Ragweed 0.1	3-4 wk.	None	95%
41	1107	40	12	Early AB Late C	1928	Timothy 0.008 Ragweed 0.1	3-4 wk.	None	85%
42	972	21	7	Late C	1928	Ragweed 0.1	3-4 wk.	None	85%
43	1333	18	5	Late C	1929	Ragweed 0.1	3 wk.	None	90%

5. When the amount of solution injected is large, we have for years injected the amount superficially in two doses, one above the other, thus obtaining larger local reactions, but fewer constitutional ones.

The dosage schedule based (according to Cooke) on the degree of sensitivity has to be modified by personal experience with the patient. Treatment of the particular patient is individual, classification being merely a guide.

CLINICAL RESULTS

Patients have now been under perennial treatment for varying periods up to ten years and the results are most gratifying.

In no case has a patient under annual treatment fared worse than with his preseasonal treatments.

The annual plan of treatment does not eliminate the necessity of an annual determination of the degree of constitutional sensitiveness, for this sensitiveness may occasionally change. We have had three patients who could not take a dose larger than 0.02, who previously had taken 0.1 mg. N. per c.c. for 20 or more doses.

Levine and Coca have confirmed this in their quantitative study of the atopic reagins. They noticed that in some cases of hay fever, while under treatment, there was an increase of the reagin content of the blood.

REMARKS

Case 4. In 1927, timothy 0.01 marked. In 1928, timothy 0.05 marked. In 1930, timothy 0.1 marked. Treated for early hay fever in 1924-25-26-27. No symptoms or treatment of early hay fever in 1928-29-30. Negative to timothy 0.01 mg. N. per c.c. solution in 1927.

Case 8. No treatment in 1925, and had bad hay fever that year.

Case 10. Tolerated maximum dose ragweed 0.08.

Case 12. Took ragweed 0.1 in 1926. Could not tolerate ragweed 0.035 in 1929-30. Test: Ragweed 0.01 moderate in 1925. Ragweed 0.01 marked in 1930.

Case 14. There is a definite maximum dose beyond which constitutionals follow.

Case 15. Son of Case 32. 1922, timothy 0.01 slight. Ragweed 0.01 moderate. No symptoms in 1922-23.

Case 16. Constitutional to timothy 0.015. Never to ragweed 0.1.

Case 17. No treatment or symptoms in 1928-29 or 30. Test: Ragweed 0.1 moderate 11/3/28. Ragweed 0.05 moderate 6/29/29.

Case 27. Took ragweed 0.1 in 1928-29, but cannot take more than ragweed 0.02, thought tests as Class C.

Case 28. Can now tolerate ragweed 0.1, previously maximum dose 0.065.

Case 34. In 1928 and 1929, maximum dose was 0.005. Now takes ragweed 0.025.

Case 36. Maximum dose ragweed 0.2 now, had taken 0.1 a year ago.

Case 40. Gives marked reaction to timothy 0.001, but no clinical early hay fever in 1929 and 1930.

We again wish to emphasize the precautions that must be observed in applying the annual treatment. They consist, first, in the careful observation of each case, while the interval between injections is being lengthened; second, in the cautious changing from an old extract to a new one.

SPECIAL ADVANTAGES OF THE PERENNIAL TREATMENT

1. The treatment may be instituted at any period of the year, merely increasing dosage to maximum, then increasing the interval as tolerance permits.
2. The actual number of visits to the office or clinic can be lessened from the usual 20 or more to 12.
3. There is little likelihood of an interruption of the treatment by illness—or absence for other causes.
4. It distributes the load of the physician's work in the clinic and in private practice throughout the year.

SUMMARY

A modification of the specific treatment of pollen hay fever is presented, consisting of a distribution of the injections at three- to four-week intervals throughout the year, instead of the usual preseasonal injections at five- to seven-day intervals.

(For discussion, see page 199.)

THE IDENTITY OF THE ALLERGICALLY ACTIVE SUBSTANCE IN THE GIANT AND LOW RAGWEED POLLEN*

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ROBERT CHOBOT, M.D.
NEW YORK, N. Y.

FORMER work[1] has shown that a water soluble albuminous protein was responsible for the allergic activity of the giant ragweed pollen *(Ambrosia trifida)*. The active substance has been separated from the low ragweed pollen *(Ambrosia artemesiaefolia)*. The weight of clinical and experimental evidence favors the view that the active substances in these two pollens are biologically identical. The present paper offers evidence to show that they are chemically similar as well as biologically identical.

HISTORICAL

Cooke and Vander Veer[2] in a study of 26 cases of autumnal hay fever found similar sensitivity to extracts of the giant and low ragweed pollen. Coca and Grove[3] employing the indirect method of testing of Prausnitz and Küstner[4] found that in every case, sites desensitized with an extract of the giant ragweed were desensitized also to an extract of the low ragweed. Walzer and Grove[5] sensitized guinea pigs with an extract of one ragweed pollen and with the Dale technic found the uterine muscle sensitive to extracts of both pollens. From clinical observations Scheppegrell[6] considered the active substance of the two pollens to be the same. Brown[7] in a study of 31 cases of ragweed hay fever found not only equal sensitivity to the extracts of the two pollens, but also equal tolerance to similar doses of extracts of the two pollens. Spain and Hopkins[8] in a study of a large number of patients and using both the direct and the indirect methods of testing failed to show any specific difference in the allergic activity of the giant and low ragweed.

Bernton[9] from clinical observations did not consider the active material of the two pollens identical. Rappaport and Johnson[10] employing the scarification method in 40 cases of ragweed hay fever failed to show identical sensitivity to protein fractions of the two pollens.

EXPERIMENTAL

a. *Chemical.*—Since a water soluble albuminous protein was found to be the allergically active material in the giant ragweed pollen, a sim-

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ilar material was prepared from the low ragweed pollen. The petroleum ether defatted low ragweed pollen after absolute, 95 per cent and 85 per cent, alcoholic washing, was extracted with distilled water, and the protein was purified by repeated precipitation with ammonium sulphate, as already described in the purification of the allergically active substance from the giant ragweed.[1] The final product was dialyzed free from sulphate, and the clear distilled water solution gave similar protein tests as the purified material isolated from the giant ragweed. It was levorotatory and gave a positive biuret and Millon's test and precipitation with picric and phosphotungstic acid. The Molisch test was negative and it contained no phosphorus. The solution after Seitz filtration contained 0.1 mg. nitrogen per c.c. Salt was added to part of the solution to 0.85 per cent concentration, and it was used in the treatment of the experimental cases described below.

Alcohol was added to the remainder of the water solution giving a flocculent precipitate which was dried at 100° C. It gave the following analysis:

N 9.10 per cent C 47.3 per cent H 6.89 per cent
residue 4.23 per cent

Percentage calculated after correcting for residue:

N 9.50 per cent C 49.4 per cent H 7.2 per cent

The analysis is typical for protein although lower in nitrogen content than the sample prepared from the giant ragweed. In this case a much larger amount of pollen was used in order to obtain sufficient material for treatments. This made purification of the product more difficult, and the analysis shows the material was not quite so pure as that prepared from the giant ragweed. It was identical with the material from the giant ragweed in all its chemical reactions.

Extracts of the purified protein albumin were prepared from the giant and low ragweed pollen under identical conditions for the desensitization tests. Thirty grams each of petroleum ether defatted giant and low ragweed pollen were treated as follows: The pollen was rapidly extracted with 500 c.c. of 80 per cent alcohol. It was filtered off on a Buchner funnel, washed with a 100 c.c. additional 80 per cent alcohol, then with ethyl ether, and air dried. This treatment as formerly shown[1] facilitated the purification of the protein. The pollen residue was extracted following the above treatment with about 200 c.c. of distilled water for eighteen hours at 7° C. After filtering, the extract measured 200 c.c. and it was saturated with ammonium sulphate. After five hours' standing, the precipitated protein was filtered off and dissolved in 100 c.c. of water. Sixty grams of ammonium sulphate were added, and the P_H was adjusted to 4.6 with 0.2 normal sulphuric acid. The precipitated protein was similarly filtered off, dissolved, and precipi-

TABLE I

COMPARISON BY DESENSITIZATION OF THE PURIFIED ALBUMINOUS PROTEIN FROM THE GIANT AND LOW RAGWEED POLLEN

JULY 29		AUG. 3			AUG. 4			AUG. 5*								
SITE	SERUM	SOLUTION USED	N. C.C. MG.	RESULT	SOLUTION USED	N. C.C. MG.	RESULT	SOLUTION USED	N. C.C. MG.	RESULT	SOLUTION USED	N. C.C. MG.	RESULT	SOLUTION USED	N. C.C. MG.	RESULT
1	Mc.															
2	Mc.	101G	0.01	++++	101G	0.01	–	101L	0.01	–	dog ep.	0.1	++++			
3	Mc.															
4	Mc.	101L	0.01	++++	101L	0.01	–	101G	0.01	–	dog ep.	0.1	++++			
1	Cor.	101G	0.01	+++	101G	0.01	+	101G	0.01	–	101L	0.01	–	orange		++
2	Cor.							101G	0.01	+++						
3	Cor.	101L	0.01	+++	101L	0.01	+	101L	0.01	–	101G	0.01	±	orange		++
4	Cor.							orange		++						
1	Ep.															
2	Ep.							101L	0.01	++++						
3	Ep.	101G	0.01	++++	101G	0.01	±	101L	0.01	–						
4	Ep.	101L	0.01	++++	101L	0.01	±	101G	0.01	–						
		July 30			July 31			Aug. 3*								
1	G.	101G	0.01	+++	101G	0.01	–	101L	0.01	–	castor bean	0.001	++++			
2	G.															
3	G.	101L	0.01	+++	101L	0.01	–	101G	0.01	–	castor bean	0.001	++++			
4	G.															
1	Fd.	101G	0.01	++++	101G	0.01	+	101G	0.01	–	101L	0.01	–	L.R.	0.1	–
2	Fd.							101G	0.01	+++						
3	Fd.	101L	0.01	++++	101L	0.01	+	101L	0.01	–	101G	0.01	±	L.R.	0.1	–
4	Fd.							101L	0.01	+++						

0.05 c.c. of the test solution was used in each and 0.05 c.c. of serum was injected into each site.
101G albumin of the giant ragweed.
101L albumin of the low ragweed.
L. R. routine extract of low ragweed.
*A forty-five-minute interval was allowed between tests carried out on the same day.

tated and taken up in 25 c.c. of water. It was dialyzed free from sulphate against distilled water, and after Seitz filtration measured 50 c.c. Nitrogen was determined using 20 c.c. for each Kjeldahl determination. The giant ragweed preparation 101G contained 0.05 mg. nitrogen per c.c., and the low ragweed preparation 101L contained 0.03 mg. nitrogen per c.c. Dilutions of each were made using buffered saline to contain 0.01 and 0.001 mg. nitrogen per c.c. These dilutions were used in the comparative desensitization tests.

b. *Biological.*—The desensitizations of the active sites were quantitatively carried out as described in the former paper[1] using the indirect method of testing of Prausnitz and Küstner.[4] In Table I are given the results with five different ragweed sensitive sera. Desensitization tests were carried out with nine different ragweed sensitive sera with the same results. Seven of the tests were done in duplicate. The results show that the ragweed sensitive sera were completely desensitized by the purified protein of either the giant or the low ragweed pollen. When the site was desensitized to the ragweed preparation, it was tested with an extract of an unrelated antigen to which it was sensitive, and a positive response indicated that the negative reaction to the ragweed was due to specific desensitization and not due to refractoriness of the site. After desensitization with the purified material from the low ragweed, 101L, a routine extract, L.R., of the low ragweed pollen gave no reaction, showing similarly to the case of the giant ragweed that a single, water soluble albuminous protein, chemically similar and biologically identical was responsible for the allergic activity of the giant and low ragweed pollen.

Twelve cases of ragweed hay fever with similar skin sensitivity were selected for therapeutic treatment. Six of the cases were treated with the purified protein solution prepared from the low ragweed pollen as described on page 120. Six cases as controls were treated in the regular manner with the routine extract (giant ragweed). One of the cases treated with the purified protein from the low ragweed had a constitutional reaction but did well, and all the cases so treated were as well protected from hay fever as were the control cases. In the final injection, the control cases were given the purified low ragweed protein of the same strength as they had received of the routine extract (giant ragweed). The cases treated with the purified low ragweed protein were given a similar dose of the routine extract (giant ragweed). No constitutional reactions resulted, showing equal tolerance to either preparation which was further evidence of the identity of the allergically active material.

Work under way in this laboratory shows a similarity in the chemical nature of the allergically active material in other pollens and dust.

SUMMARY

A water soluble albuminous protein isolated from the giant and the low ragweed pollen was found to be chemically similar and biologically identical.

Therapeutically, the purified protein from the low ragweed pollen was as effective in the treatment of hay fever as a routine extract of the giant ragweed pollen.

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EMANATIONS OF FLIES AS EXCITING CAUSES OF ALLERGIC CORYZA AND ASTHMA

III. Hypersensitiveness to Moths and Butterflies *(Lepidoptera)**

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IN THE preparation of my recent papers on the caddis flies[1, 2] it was necessary to consult a number of textbooks and monographs on flies so as to familiarize myself with their structure, life habits and general distribution. Several authors[3, 4, 5, 6] pointed out that the caddis fly is closely related biologically to moths and butterflies. The very generic names of these flies suggested a striking similarity. The sand fly belongs to the order of *Trichoptera* which is derived from two words, *trichos* meaning hair, *ptera* meaning wings. Moths and butterflies are grouped together under the order of *Lepidoptera, lepido* meaning scale, *ptera,* wings. Writers of insect life have long recognized the abundance and ease with which desquamations are thrown off by these flies. Moreover, every one who has had the occasion to pick up a butterfly or moth, well remembers the dust or powder which comes off the wings.

With these facts in mind, it occurred to me that these hairs and scales of moths and butterflies could be found in the air in sufficient quantity to affect man in a manner similar to that of sand flies, that is, these emanations could be absorbed chiefly through inhalation and cause allergic symptoms. At this time, I wish to present a study of these flies which will include a brief consideration of their anatomic structures, life habits, microscopic examinations of their emanations, evidence of their widespread distribution, and finally a preliminary report of several cases of hypersensitiveness to moths and butterflies.

While a large amount of literature has been contributed on the life habits and economic importance of moths and butterflies, there has never been mentioned the possibility that these flies might cause any ill-effects to human beings. The wide distribution of these flies is shown by the fact that over 600 species of butterflies and about 9,000 species of moths have been found in North America.

Butterflies have always been attractive because of the beauty of the color schemes which are found on their bodies and wings. Fur-

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thermore, they do not cause any damage to farms, gardens or any other economic loss to man. A great number of people are exposed to these flies during the summer months. It may be the farmer or the vacationist in the country, the lover of gardens, the cultivator of flowers or the grower of fruit trees (Fig. 1). Others are engaged in collecting specimens for museums and schools, mounting specimens for pictures, art pieces, jewelry, etc.

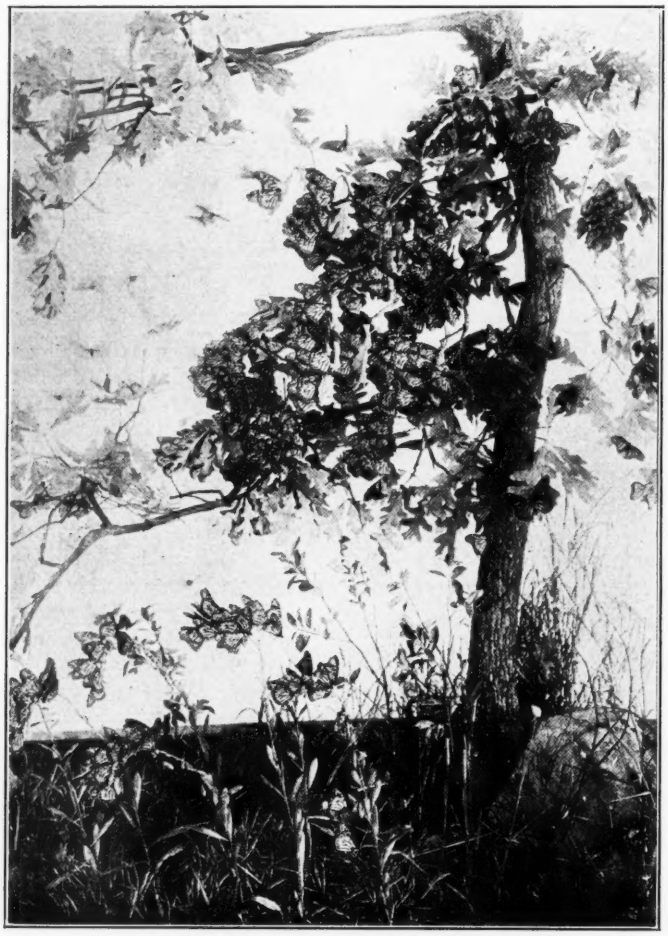

Fig. 1.—A swarm of monarch butterflies. Great numbers of these common butterflies are often seen together in the field, on farm or in any of the city parks. The emanations from their wings constitute a new and heretofore unsuspected excitant of allergic symptoms. (Courtesy American Museum of Natural History.)

Moths have a greater distribution. About 100 species are known to be pests which cause an enormous economic loss each year. There is the coddling moth which destroys many peach crops. In the garden, the moth will attack the stalk and vegetable. The miller moth is known to ruin a crop of grain and make flour unsuitable for consumption. In the home we find the familiar clothes moth which does much

damage to clothes, furniture, rugs, etc. I have often seen them together with swarms of sand flies and even with May flies near the lake and river. Most moths are active during the late afternoon and evening, and like sand flies, they are attracted in great numbers to artificial lights of any source (Figs. 2 and 3).

Fig. 2.—The common clothes moth. This familiar fly is the cause of millions of dollars of damage to clothes, furniture, rugs, etc., every year. In addition, it sheds considerable "dust" which on inhalation can cause asthma or hay fever. This moth resembles the sand fly very much in size and shape.

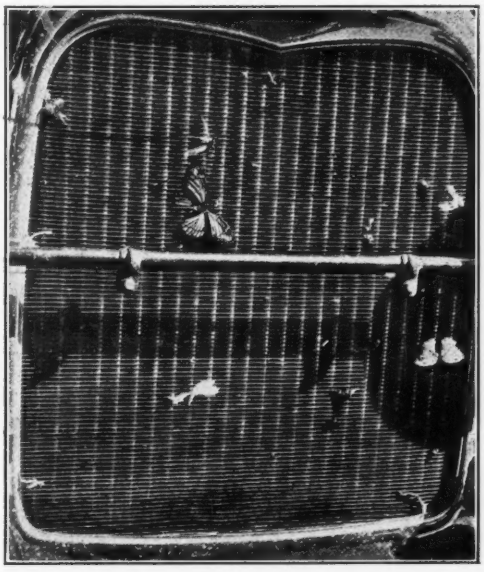

Fig. 3.—A common method of contact with flies. A short auto ride through the country or the city parks brings one in contact with swarms of sand flies, moths and butterflies. Striking the radiator or windshield, they throw out a considerable amount of emanations which may cause allergic symptoms to the driver or passengers.

Nevertheless, the preponderant number of moths are harmless and as attractive as butterflies. In one instance, man has domesticated one of them, the common silk moth. The silk in the cocoon spun by the larvae of this moth has given us one of our oldest industries.

CHART I

1. Common name	Caddis fly	Moth	Butterfly
2. Name of order	Trichoptera	Lepidoptera	Lepidoptera
3. Metamorphosis	Complete—worm to adult fly	Complete—cocoon to adult moth	Complete—cocoon to adult fly
4. Distribution	Very abundant near rivers, lakes and ponds	Very abundant and widespread in city and country	Very abundant about gardens, fields and parks
5. Duration of adult life	Usually 24 hours	24 hours to 4 to 5 weeks according to species	Average 4 to 5 weeks
6. Time of year when seen	June to September	June to October	Latter part of May to October
7. Time of day when seen	Mostly late afternoon and evening	Day and night	Daytime only
8. Emanations	Hair and epithelia readily air-borne	Hair and epithelial scales readily air-borne	Hair and Epithelial scales readily air-borne.
9. Immunologic relation to man	Causes allergic symptoms chiefly through inhalation of emanations	Same	Same

In the accompanying chart, I have compiled a list of the characteristics of these three flies which may be of interest to the allergist. The minute structure of these flies and their emanations are described in the accompanying photomicrographs (Figs. 4 to 8). The emanations are called setae, which vary in shape from the long slender hair to the

Fig. 4.—Adult moth (owlet). This photomicrograph illustrates the immense amount of "dust"—emanations which are thrown off by one of the common moths. Note portions of wing which are made bare by the expelled scales.

typical scales which cover the wings like shingles on the roof of a house. A single moth like the butterfly or sand fly is capable of losing a large amount of these scales (Fig. 5). I believe that more scales and hair are cast into the air by a single moth than the amount of pollen which is blown from the stamen of a timothy grass over a similar period of time. (Compare Figs. 5 and 9.)

A comparison with the distribution of the common pollens in the air should give us a fairly reliable criterion as to the extent in which the emanations of these flies are found and, in like manner, are capable of producing allergic symptoms. I, therefore, referred to a collection of pollen plates which I had exposed and studied during the years 1925, 1926, and 1927.[7] Reexamination was made of the glass

Fig. 5.—Wing of an owlet moth. This photomicrograph readily demonstrates the large amount of so-called "dust"—emanations which are thrown into the air by a single moth.

slides which had been exposed on the top of an office building (over 300 feet from the street level), the main corridor of another office building in the business section of Buffalo, several parks and hospitals, in fact, all the common places where people gathered either for work or for pleasure. The results of these examinations showed that, first, the emanations were found in the air during the months of June, July,

August and September; second, the amount of hair and scales on some days corresponded closely to the amount of pollen found on the glass slide; third, these emanations were found at various places about the city and country where people usually assemble. The sand flies predominated in the city while the scales of moths and butterflies were more abundant in the suburbs and rural districts (Figs. 10 and 11).

Fig. 6.—Emanations of moth. Photomicrograph showing hairs and scales as shed by wing of the owlet moth. These emanations are similar to those which are thrown off by butterflies.

Further evidence as to the widespread distribution of the emanations of moths and butterflies has been noted. Our summer home is located about 20 miles from Buffalo, Niagara River and Lake Erie. Sand flies or May flies have never been found near the house or farm. The house was closed last fall for the year. Early in March of this

year (1931), I opened the house to collect a sample of the house dust. Examination of this dust showed the typical scales of moths and butterflies (Fig. 12). It is my belief that this factor in house dust presents another new excitant of allergic symptoms.

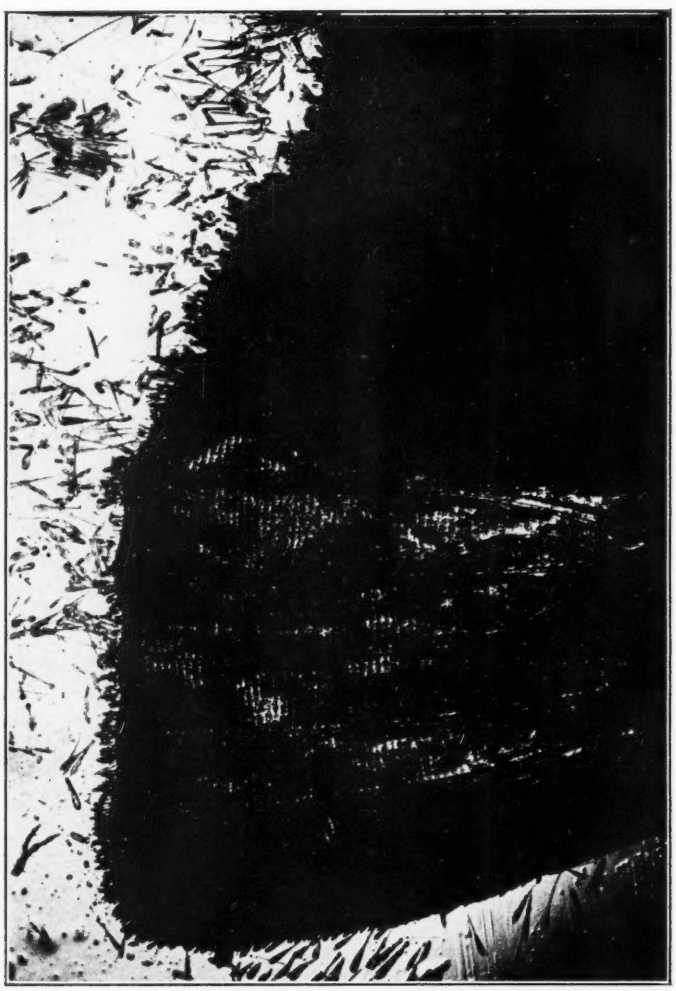

Fig. 7.—Wing of cabbage butterfly. This butterfly is one of the commonest of all flies. Note the hair on the rim of the wing. The bare spots are evidence of epithelia which have been thrown into air during its flight and by handling when mounted.

CASE REPORT

Mrs. C. P. P. consulted me early in the summer of 1928. She suffered typical hay fever symptoms of moderate severity. Every summer since 1924, she experienced the same symptoms while living at her summer home which was located near Lake Ontario. She was better when she stayed in the city. Repeated tests with the routine extracts gave negative reactions. Even raw grass and ragweed pollen

dropped into her eye and nose failed to elicit a reaction. She had a very large and beautiful garden in which 33 varieties of flowers were cultivated. She spent a great deal of her time in her garden. Glass slides were, therefore, exposed about her home to determine if pollen from any of the flowers could be found in the air. Only the pollens of three species of flowers were discovered on the glass slides. These flowers were then uprooted but there was no improvement in her condition. In March, 1931, I again examined those glass slides and found

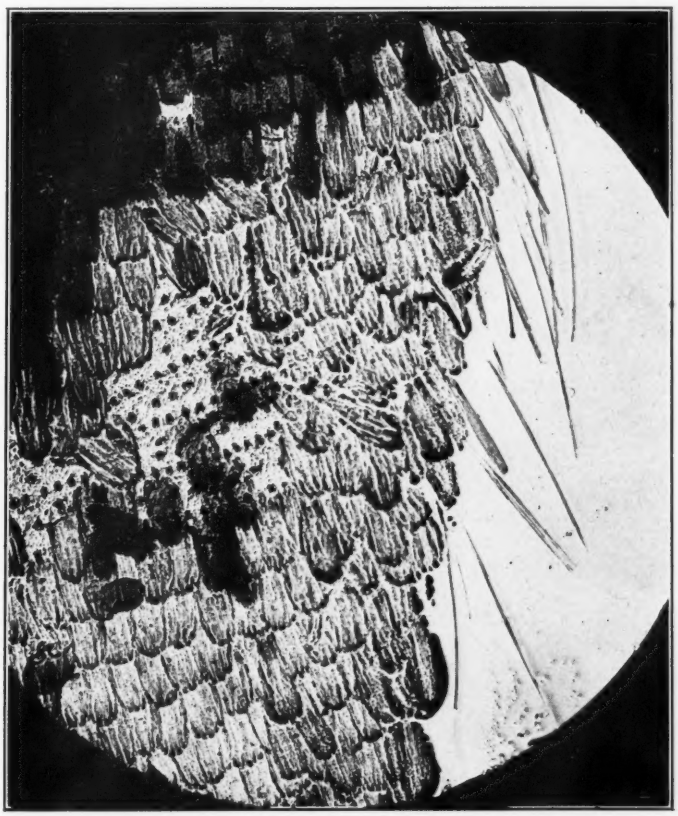

Fig. 8.—Wing of butterfly. Photomicrograph showing more detailed structure of the wing. The hairs are seen along its side. The characteristic arrangement of the scales resembles shingles on a house roof. Some of the scales can be seen already freed of their attachments. The bare spot is again evident; each black dot is a little socket in the wing in which an epithelial scale had once been attached.

a comparative large amount of hairs and scales which belong to moths and butterflies (Fig. 13). In view of this positive finding, the negative reactions to complete routine tests, her work in the large garden where moths and butterflies would be found, her feeling better in the city, it is reasonable to assume that the emanations of these flies could be the cause of her hay fever symptoms. As soon as I have the opportunity, I hope to test her with the extracts of the wings of moths and butterflies.

An extract of the wings of several species of butterflies and an extract of the wings of moths were prepared according to the method of Coca and Milford.[8] Having in mind the structural similarities which these flies have to sand flies, I have made preliminary tests on six of my cases which are known to be sensitive to sand fly. Four of these six patients gave positive skin and eye reactions to the extracts of

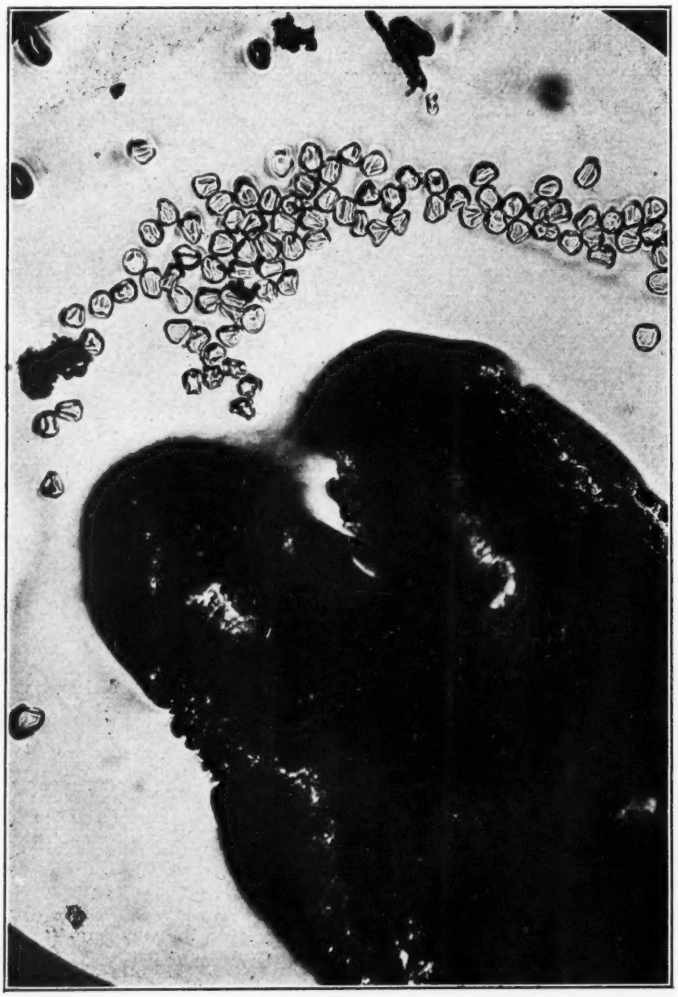

Fig. 9.—Anther and pollen of timothy grass. This photomicrograph of an anther of timothy grass discharging its pollen is shown to serve as a contrast to Fig. 5. It is quite evident that the moth is capable of shedding more epithelial scales than an ordinary grass stamen produces pollen grains.

moths and butterflies, the remaining two, a moderate skin reaction only. A little "dust" from the wings of moths and butterflies was placed on the conjunctiva of these four reactors. An immediate and distinctly positive reaction was produced in the eye. Ten cases known to be sensitive to pollen of grasses and ragweeds and fifteen sensitive

to other air-borne allergens, such as cat hair, feathers, orris, etc., were used as controls. They were all negative. Five individuals who have no history of allergy were also tested in the skin and eye. Negative reactions resulted. Incidently our office technician was among those who were first tested. She was to be used as a control because she had never given me any history of allergy. Much to our surprise, we found that she was quite sensitive to both moths and butterflies. She

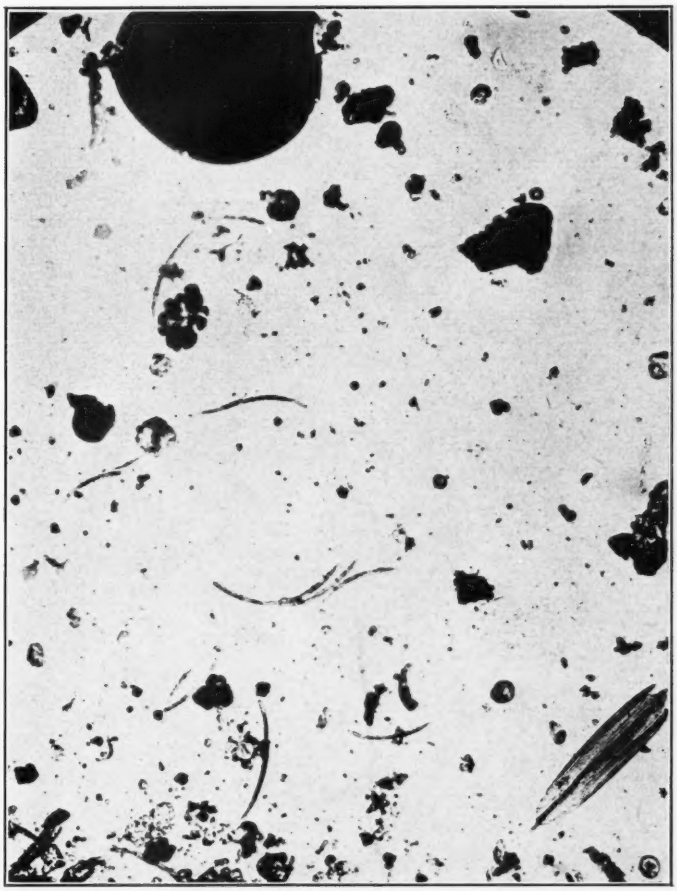

Fig. 10.—Glass slide exposed on a summer day on top of Buffalo's tallest building. A typical scale belonging to a moth is seen along with sand fly hair.

verified the positive skin and eye tests by reporting a distinct tickling of the nose with typical paroxysms of sneezing while preparing the flies for extraction. Passive transfer tests which were made with her blood serum were positive. The wheal which was produced upon the sensitized site of the normal person by the injection of 0.03 c.c. of the butterfly 0.01 mg. extract was just as large as the one which was formed in the hypersensitive individual. Routine tests with these extracts will be made on all new patients, particularly on those whose

symptoms occur during the summer months. This data will be reported in a later paper.

SUMMARY

1. The similarity in the structure of the emanations of sand flies, moths and butterflies has been demonstrated.

Fig. 11.—Glass slide exposed near window of one of Buffalo's hospitals during the month of July. This photomicrograph well shows that the scales and hair of moths and butterflies are found in the air in great abundance.

2. The emanations of these flies have been shown to be readily air-borne during the months of June, July, August and September throughout the city and rural districts. The amount of distribution compares favorably on certain days with that of the common pollens.

3. A preliminary report is submitted of a case of hypersensitiveness to the hair and scales of moths and butterflies. Four other patients

Fig. 12.—Photomicrograph of glass slide upon which has been blown some dust which had been collected from the rug in a farmhouse. Here are shown two epithelial scales from one of the many moths which are found in the rural as well as urban parts of our country.

Fig. 13.—Photomicrograph of glass slide exposed July 24, 1928, at the summer home of a patient suffering with summer hay fever. Reexamination in 1931 showed very little of the common pollens but an abundance of emanations of moths and butterflies—a possible cause of her hay fever.

gave positive skin and eye reactions to extracts of these flies. It is believed that two new excitants of allergic manifestations have been found. There is a possibility that the atopic agent of the sand fly is identical or at least closely related to that of moths and butterflies.

4. There is ample justification for delving more into this great field of flies for the exciting cause of hay fever and asthma which occur during the summer months, especially for those cases which do not respond so well to our usual forms of treatment.

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(For discussion, see page 204.)

THE MECHANISM OF AN ASTHMATIC ATTACK IN CHRONIC ALLERGIC ASTHMA*†

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AN ATTACK of allergic asthma is generally assumed to be produced by one or more of the following three factors: (1) spasm of the bronchial smooth muscle, (2) swelling due to exudation into the bronchial mucosa, (3) bronchial occlusion due to mucous gland secretion. The determination of the exact mechanism that brings about an asthmatic attack is more than of an academic interest. The solution of the problem will undoubtedly throw further light on the etiology and the treatment of the condition. The evidence available at the present of the responsibility of any of the three factors mentioned is only circumstantial and indirect. The bronchospasm conception finds support in the following observations and deductions: 1, bronchi are capable of contraction; 2, bronchial contractions can be elicited by various proteins; 3, bronchial constriction occurs upon vagus and sympathetic (?) stimulation; 4, bronchospasm causes death in guinea pigs in anaphylactic shock; 5, presence of distended lungs in guinea pigs dying of anaphylaxis and presence of pulmonary emphysema in asthmatic individuals; 6, an asthmatic attack may be initiated by sensitizing proteins; 7, some types of asthmatic attacks have a very sudden onset; 8, there is hypertrophy of the bronchial musculature in asthmatic patients.

Bronchial contraction is one of the protective reflexes of the lungs, and presence of foreign material in the bronchi promptly initiates such contractions. My experiments (unpublished) resulted in similar findings. In the presence of such a sensitivity of the bronchial mucosa it is not surprising to find that it responds to substances which are well-known stimulants. The subject of vagus and sympathetic stimulation is still too much in the process of crystallization to draw any references in relation to an asthmatic attack. We do not know whether in asthma nerve stimulation actually occurs, and there is even divergent testimony as to which nerve is the constrictor and which is the dilator. It is unfortunate that the acute alveolar hyperdistension in the anaphylactic guinea pig had been compared to human asthmatic emphysema. Both anatomically and functionally, the two processes are unlike. If the hyperdistension is due to broncho-

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constriction, which is doubted by some (Hoover), and if it were possible for the guinea pig to live for two to four hours with such a continuous bronchoconstriction, this apparent emphysema of the lung would become a massive atelectasis. There is sufficient and trustworthy experimental data (from Lichtheim[1] 1879, to Coryllos and Birnbaum[2] 1928) demonstrating that total and sudden occlusion of the bronchi produces atelectasis and not emphysema. Lichtheim showed that air will disappear from lung tissue in two to four and a half hours after complete obstruction of its bronchus. That a sensitizing protein may start an attack is true, but the fact does not prove anything. Many sudden changes may occur that are not necessarily that of bronchoconstriction. It is difficult to conceive that the bronchial musculature would hypertrophy from occasional attacks of spasmodic contractions. Figley and I advanced the conception that the muscle hypertrophy is that of work and is due to the prolonged efforts of the bronchi to expel the mucous plugs. We compared the bronchial hypertrophy to that of the heart which thus compensates to an additional load.

The conception of mucosal edema being responsible for an asthmatic attack is on less firm ground than the bronchoconstriction theory. The evidence is almost entirely inferential. The following observations are advanced: 1. A local edema of the skin occurs upon application of a sensitizing agent. 2. Allergic nasal mucosa becomes edematous in hay fever or upon contact with pollen. 3. Urticaria and angioneurotic edema may be associated with asthma. 4. Edema and swelling of bronchi are found postmortem. 5. Hyperemia of bronchial mucosa was observed by means of the bronchoscope during an asthmatic attack (Pieniazek,[3] Nowotny,[4] Ephriam[5]). An edema of the bronchial wall is very frequently found in asthmatic persons who died during an attack. This edema, however, is not evanescent and does not occlude the bronchial lumen. Contrary to existing views the lumen is not appreciably narrowed. The edema is likely a part of the general peculiar inflammatory reaction present in the bronchial wall. Alexander[6] points out that not all the observers found bronchial edema with the bronchoscope; they failed to consider the effect of the local anesthetic, and some of the cases examined were that of chronic bronchitis.

The third theory is that of an excessive secretion of mucus by the bronchial glands and consequent plugging of the lumina. The following evidence is presented to substantiate this conception: 1, Most of the medium and small bronchi are completely occluded in asthmatic individuals who died during an attack (Huber and Koessler,[7] Steinberg and Figley[8]); 2, bronchoscopic observations of large collections of mucus in the bronchi during a paroxysm (Freudenthal[9]). Since

many types of asthmatic paroxysms occur apparently promptly after exposure to the sensitizing substance, it is not held probable that mucus could be secreted in sufficient quantities rapidly enough to produce bronchial closure. That mucus is secreted and plugs the bronchi cannot be denied, but this secretory activity may possibly follow the attack and not necessarily initiate it.

The purpose of this work was to determine if any additional information of the mechanism of an asthmatic attack could be secured. Roentgenologic study was made of lungs injected with lipiodol of asthmatic patients during an attack, shortly following it and during apparent freedom from attacks. These roentgenologic studies were correlated with the pathologic material in the literature and that of my cases.

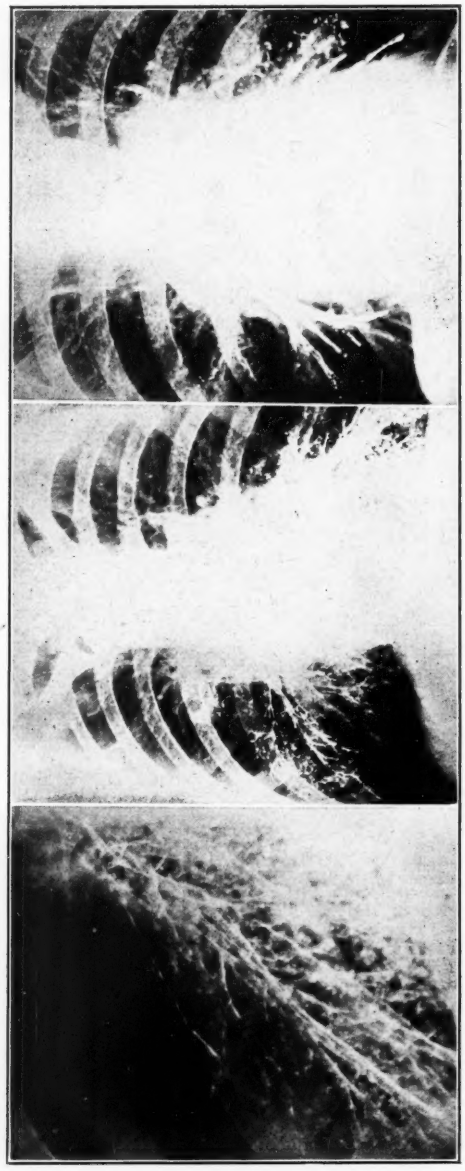
Lipiodol was injected into the bronchi of normal people and roentgenograms were made. The bronchial tree was well delineated, arborization was distinct and profuse. (Fig. 1 *A*.) The profuseness of the tree varies with the age of the patient and incidence of bronchial infection, being less profuse in the old and in those with repeated bronchitic attacks. Lipiodol injections were then made in asthmatic individuals with attacks of varying severity and of varying duration of asthma. In those patients with a short asthmatic history, the bronchial tree showed only a partial involvement during or a few hours following the peak of an attack. The lipiodol did not fill completely the bronchial tree; there was a clear-cut demarcation between the injected and the uninjected bronchi and the bronchial wall was straight. Uninjected areas were present between visualized parts of the same bronchus. In one instance one side of the chest (right) was only involved (Figs. 1 *B* and 2 *A*). That one side of the chest only can be affected is of interest and has been noted previously. Levy-Dorn[10] observed in some patients a marked difference in the x-ray shadows of the two lungs during an attack, and Siegel[11] thought that the difference in involvement was due to an irregular distribution of the rhonchi. In patients with a long-standing history of asthma, the greater part of the bronchial tree was not visualized with lipiodol. The injected bronchi were sharply demarcated from the uninjected, the bronchial lumina were dilated and the walls were straight (Figs. 1 *C*, 2 *B*, 2 *C*). Apparently the severity of the attack is coincident with the extent of visualization of the bronchial tree.

The following are illustrative case histories:

1. A case of slight severity and short duration. C. P., male, aged twelve years. The first attack of asthma at the age of ten years. Eczema between six months and two and one-half years. Sensitive to ragweed, chicken, duck and goose feathers. Father had asthma.

Two other children have eczema. Lipiodol injection was done a few hours after the peak of an asthmatic attack of moderate severity.

2. A case of moderate severity. H. S., male, aged forty-nine years.

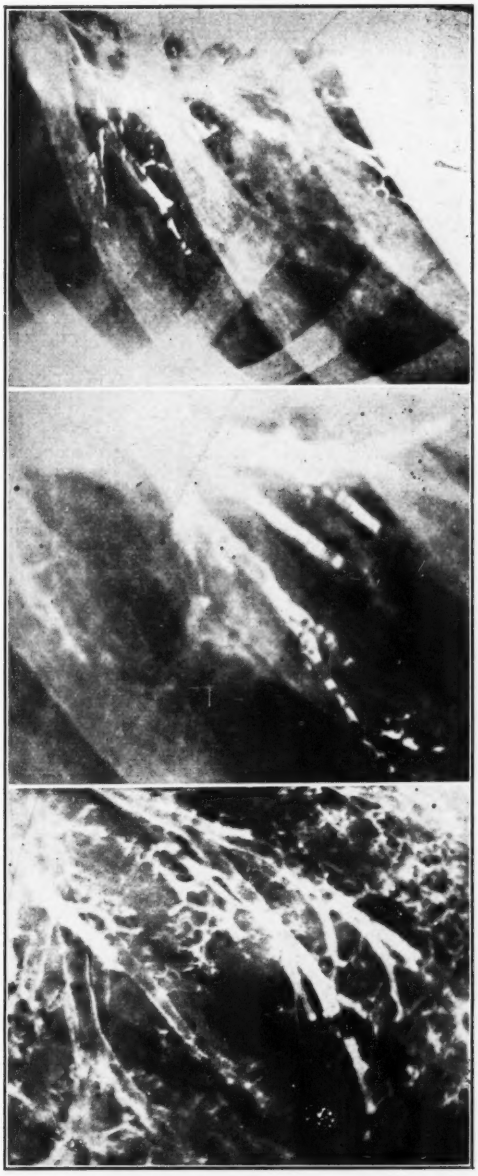


A. *B.* *C.*

Fig. 1.—*A*, A roentgenogram of a normal bronchial tree with lipiodol. The bronchi are well outlined, the arborization is distinct and profuse. *B*, A roentgenogram of bronchi showing slight to moderate involvement and only on one side of the lungs. *C*, A roentgenogram showing a marked involvement with practically complete closure of the bronchial tree.

Asthma for twenty-two years. Attacks every fall. Susceptible to house dust, dog hair and ragweed. Patient's father had asthma and his daughter has asthma. Lipiodol injection was done six to seven hours following the peak of an attack.

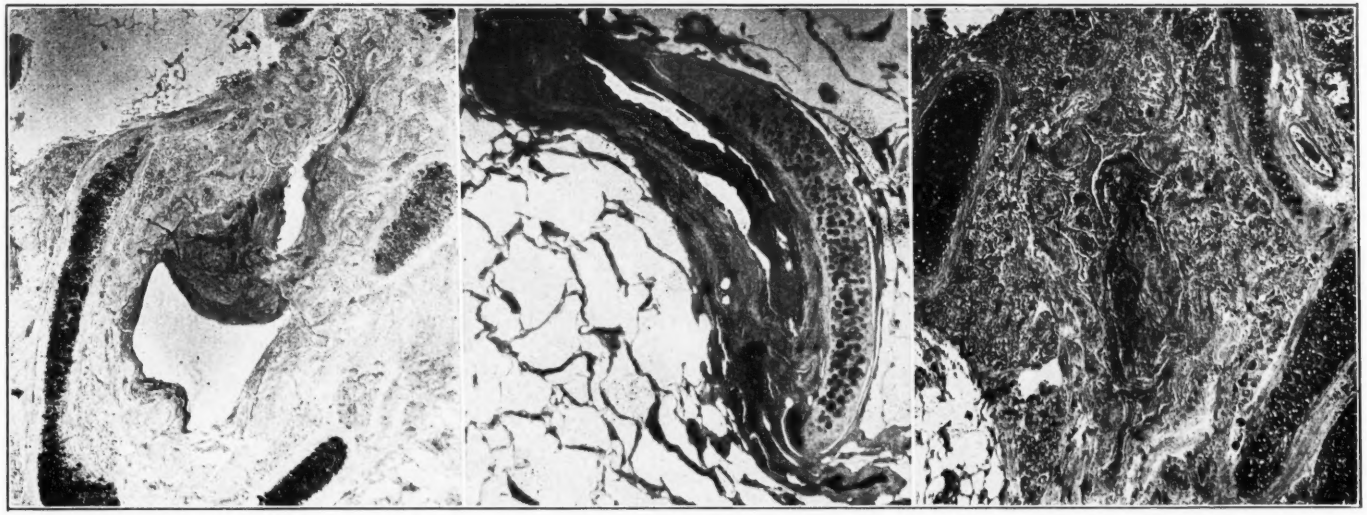
3. A severe case. H. S., male, aged fifty-four years. The first asthmatic attack at the age of fifty years. He is sensitive to ragweed. Lipiodol injection was done four days after a marked paroxysm with less severe attacks extending up to a few hours before injection.



A. *B.* *C.*

Fig. 2.—*A.* A high magnification view of a roentgenogram showing partially and completely plugged bronchi. *B.* A high magnification view of the sharp line of demarcation between injected and uninjected bronchi. Note the partially occluded bronchi and the straight walls. *C.* A high magnification of lung in a severe paroxysm. Note the almost complete lack of visualization of the bronchi.

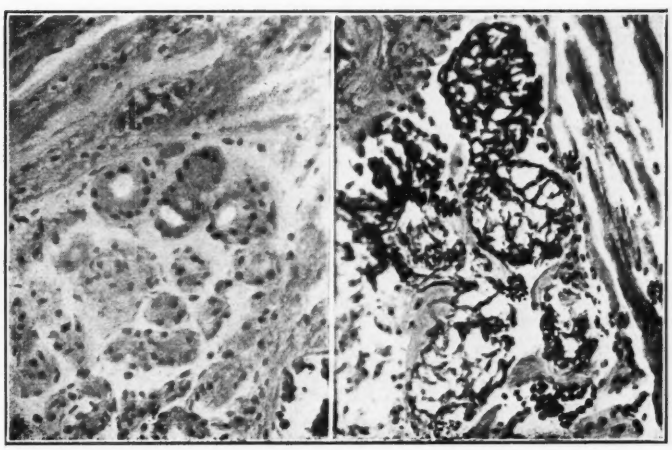
It is apparent that during an asthmatic paroxysm there is an interference with the proper filling of the bronchial tree as demonstrated by the failure of visualization of lipiodol. The extent of this lack of bronchial filling is proportionate with the severity of an attack, dura-



A. *B.* *C.*

Fig. 3.—Sections of lung from patients dying of allergic asthma. *A.* A bronchus partly filled with mucus which is fairly easily removed. *B.* A bronchus practically completely filled with mucus which can be removed with some difficulty. *C.* A bronchus completely filled with thick mucus which cannot be dislodged.

tion of asthma and frequency of previous paroxysms. In order to determine whether such a roentgenologic picture could be obtained by plugging the bronchi, an animal experiment was resorted to. With a bronchoscope, a 4 per cent suspension of gum tragacanth (which has the consistency of very thick mucus) was introduced into the right bronchus of a dog. Following the gum tragacanth, lipiodol was injected into the left and right bronchi and roentgenograms were made. The left lung showed a diffuse and uninterrupted arborization. The bronchial tree of the right lung did not fill completely, and the greater part of the bronchi was not visualized. There was a sharp line of demarcation between the uninjected and injected bronchi. The postmortem examination of the lungs revealed a complete occlusion by the gum tragacanth of the larger bronchi on the right side.



A. *B.*

Fig. 4.—Sections of lung tissue showing mucous glands. *A.* Mucous gland from a normal lung. *B.* Mucous glands from the wall of a bronchus of a patient dying during a paroxysm. Note the extensive mucus and the hypertrophy of the glands.

It is evident that complete occlusion of bronchi with a thick gummy substance results in roentgenologic pictures of lipiodol injected bronchi similar to those obtained in asthmatic patients shortly after the peak of an asthmatic paroxysm.

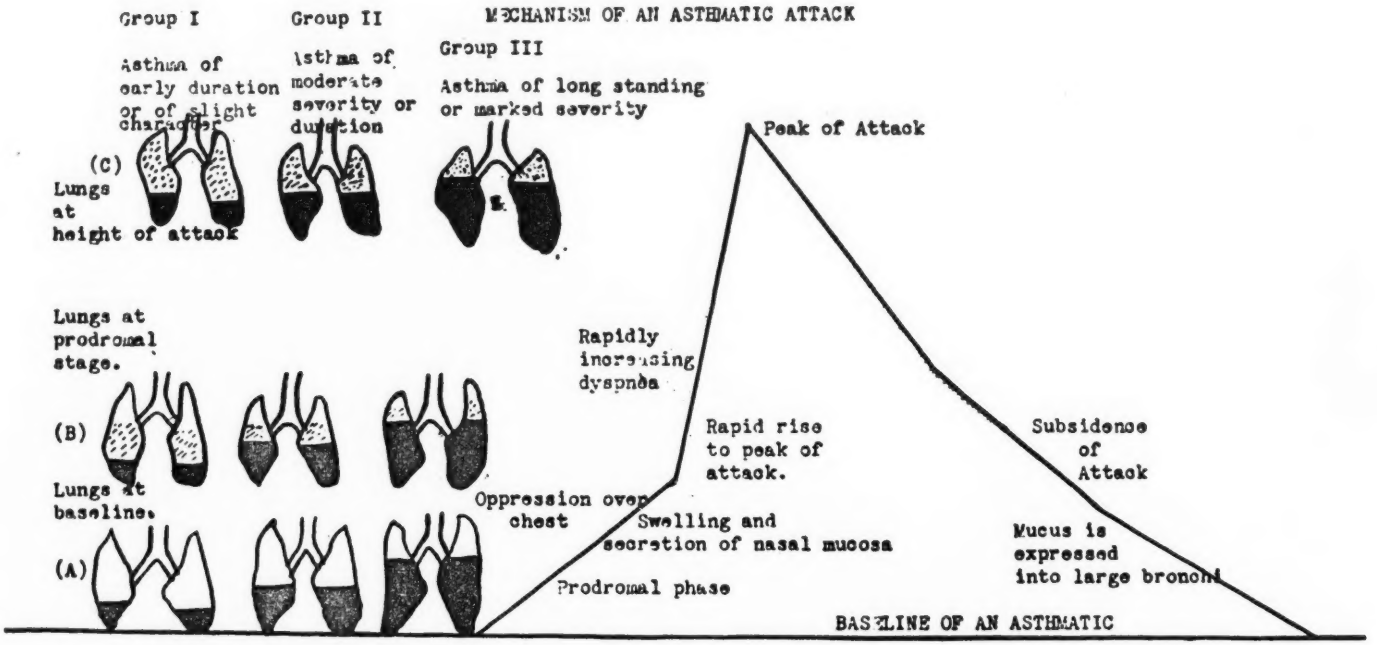
Lipiodol injections of the bronchi and roentgenograms were made of patients after they were free from attacks for a month or more. The general visualization of the bronchial tree in those patients was diminished. Some of the medium-sized bronchi were not visualized at all, and there were occasional patches of lung tissue free of lipiodol. The lack of visualization was more or less proportional with the duration of asthma, severity and frequency of paroxysms.

A study was made of the autopsy protocols found in the literature and of my cases in an attempt to correlate the postmortem with the roentgenologic findings. In the admirable critical summary of Huber

SCHEMATIC REPRESENTATION

OF THE

MECHANISM OF AN ASTHMATIC ATTACK



At the baseline (between attacks) part of lung reveals permanent occlusion of bronchi. This occlusion is denoted in heavy black. In the prodromal stage the bronchi gradually begin to fill with mucus (B). At the height of the attack the greater part of the bronchial tree is occluded by mucous plugs. This occlusion is denoted by dotted lines on the diagram (C).

Fig. 5.

and Koessler which covers the literature up to 1922, a prominent and consistent finding is a partial or complete plugging of the bronchi with mucus. In two of my cases in which death occurred during a paroxysm, practically all the small and medium sized bronchi were found to be completely occluded by firm mucous material so that it could not be dislodged even with considerable force. The mucus in most of the bronchi was lodged firmly and extended in the form of a branching tree, filling the bronchi of the lung. In some medium and larger bronchi the mucus filled the lumina only partly and could be fairly readily dislodged. It was assumed that the firm mucus which resisted removal indicated an occlusion of long standing and the partially filled lumina with fairly easily removable mucus signified a recent filling (Figs. 3 *A*, 3 *B*, 3 *C*). Associated with the plugging of the bronchi there were found hypertrophic and hyperplastic mucus-secreting glands (Fig. 4 *B*).

COMMENT

From the correlation of the roentgenologic and postmortem findings it is assumed that the failure of visualization of the bronchial tree is due to plugging with mucus from hyperfunctioning mucous glands. Since the severity of the duration of a paroxysm is inversely proportional to the degree of visualization of the bronchial tree, it may be assumed that the extent of bronchial plugging by mucus determines the character of an attack. Another determining factor is the amount of bronchial tree which is permanently occluded during previous attacks. That this factor is present is deduced from the diminution of the bronchial visualization between attacks and in the presence of mucus in the bronchi which cannot be dislodged. Fig. 5 illustrates graphically this conception.

The possibility of bronchial constriction is not denied. It may be a factor in the causation of a paroxysm, but more evidence must be supplied before bronchoconstriction can be accepted. It may be assumed that an attack is ushered in by bronchospasm but all the evidence is against bronchoconstriction being responsible for the entire trend of events preceding and following the peak of an attack.

SUMMARY

1. Lipiodol injections of bronchi and roentgenograms were made during the course of an asthmatic attack and during an interval between attacks.

2. Postmortem material of patients dying from allergic asthma was correlated with the roentgenologic findings.

3. An asthmatic paroxysm is essentially due to bronchial occlusion by mucus as a result of a hypersecretory activity of the bronchial mucous glands.

4. The degree and the duration of an attack are proportionate to the extent of mucous secretion and bronchial plugging.

5. There is a reduction of functioning lung tissue due to a permanent bronchial occlusion. The extent of this reduction is proportionate to the duration of the disease, the severity and the frequency of the individual attacks.

NOTE.—I want to express my gratitude for the invaluable aid in this work of Drs. Karl D. Figley, E. G. Galbraith and Murray E. Goodrich.

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(For discussion, see page 212.)

CONGENITAL PROTEIN HYPERSENSITIVENESS*

Protein Hypersensitiveness Transmitted From Allergic Mother to Child

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ROSENAU and Anderson[1] first drew attention to the fact that hypersensitive guinea pigs transmitted a passive sensitiveness to their offspring. The work of Otto,[2] Lewis,[3] Schenck,[4] Ratner, Jackson and Gruehl[5] corroborated this observation. Wells[6] found that offspring of guinea pigs fed oats during pregnancy were born sensitive to oats. Ratner and Gruehl[7] further showed that offspring of animals in whom asthma was induced through inhalation during pregnancy were sensitive at birth and manifested symptoms of asthma or "respiratory anaphylaxis" when brought into contact with antigenic dusts. From these studies it is evident that pregnant animals sensitized by artificial means such as injection or by natural means such as ingestion or inhalation can readily sensitize their offspring in utero.

The above experimental work on congenital sensitization lends background to the human side of this problem with which we are here primarily concerned. This phase of the problem remained untouched until Ratner[8] showed that the human fetus could be sensitized in utero through the overindulgence of protein foods consumed by a pregnant woman during the latter months of pregnancy. It will be recalled that in these instances the pregnant woman remained nonallergic. She merely served as a means of transmitting unaltered antigens to the fetus via the placenta, the offspring as a result developing a state of active hypersensitiveness.

In the present communication we shall add further to this problem by showing that the human fetus can be sensitized by an allergic mother in the same manner as occurs with the guinea pig. Certain difficulties are inherent in the study of clinical material, but we do believe that enough scientific evidence is here presented to warrant placing the human phase of congenital hypersensitiveness on as sound a basis as was done with the lower animal.

CLINICAL AND EXPERIMENTAL DATA

Studies on Family S.—General history: Mother S, twenty-six years of age, suffering from eczema, hay fever and asthma, and her child

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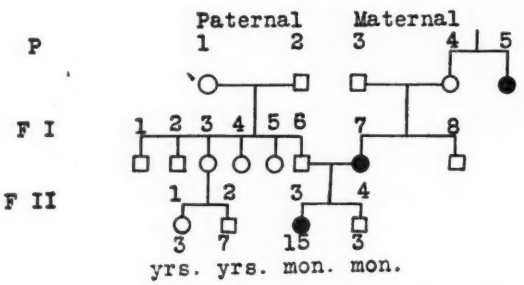
fifteen months of age, suffering from severe eczema, presented themselves for study. The mother had eczema and asthma for the past twenty-three years. When she was a child, she lived in a small town and recalled that there were many dogs, cats and horses and that she was practically always ill with asthma and eczema. Later she developed hay fever. During the pregnancy with her first child her asthma and eczema were severe. During this first pregnancy she recalled taking excessively of milk, vegetables, and had a definite craving for peanuts. Her first child whom we shall call sensitive child No. 1 developed eczema at four months, after being given a milk formula; this became progressively worse, and at fifteen months involved her entire body. The non-sensitive child No. 2 was four months of age at the time we first saw him, but he suffered no allergic symptoms. The mother's



P,F I - 1st generation, 2nd generation etc.

P 5 - maternal grandaunt (asthma)
F I 6 - father S (normal)
F I 7 - mother S (asthma,hay fever,eczema)
F II 3 - child #1 (eczema)
F II 4 - child #2 (normal)

■ ● - allergy
□ ○ - no allergy

Chart 1.—Family S.

asthma and eczema were much less severe during this second pregnancy, and she stated that during this period she had no cravings and ate much less of the green vegetables and milk than during her first pregnancy. This family has been observed for more than one and a half years, and a marked improvement resulted after a careful elimination of the sensitizing elements in the environment and food of both mother and child. The second child who is two years of age at the present time still remains nonallergic.

Hereditary Background.—The hereditary background is represented in Chart 1. It will be noted that the paternal side appears to have no evident allergy; and that on the maternal side, besides the two patients, the sister of the grandmother had asthma.

General Laboratory Findings.—There is nothing of note in the general laboratory studies (blood chemistry, x-ray, urine, cytology) except

that Mother S had an eosinophile range of 8.5 per cent to 10.5 per cent; her eczematous child, 0.5 per cent to 3.5 per cent; and the non-allergic child, 0.5 per cent to 2.5 per cent.

Protein Skin Tests.—Table I presents the results of the protein skin tests. We have divided the positive reactions obtained into three groups. In Group I are those proteins to which both mother and child No. 1 reacted. In Group II are the tests to which the mother alone reacted, and in Group III are the proteins to which child No. 1 alone reacted.

TABLE I

PROTEIN HYPERSENSITIVENESS IN FAMILY S

PROTEIN ANTIGENS	ALLERGIC SKIN REACTIONS			GROUP
	MOTHER	CHILD I	CHILD II	
Wheat proteins	+	+	–	
Egg white	+	+	–	
Veal	+	+	–	I*
Horse dandruff	+	+	–	
Feather proteins	+	+	–	
Ragweed	+	–	–	
Cattle hair	+	–	–	
Cat hair	+	–	–	II†
Dog hair	+	–	–	
Certain fruits and vegetables	+	–	–	
Fish	+	+–	–	
Beef, beef serum	–	+	–	
Cow's milk	–	+	–	
Peanut	–	+	–	
Chicken	–	+	–	III‡
Peas, squash	–	+	–	
Potato	–	+	–	
Ext. pillows and mattress	–	+	–	

*Specific antibodies (Prausnitz-Küstner) were found in the blood sera of mother and child No. 1 to all proteins in Group I. None were present in blood serum of child No. 2.

†Antibodies to dog hair were found in the mother's blood serum and not in child No. 1's blood serum. No others were studied.

‡Antibodies to peanut were found in child No. 1's blood serum and not in the mother's blood serum. No others were studied.

In Group 1 are reactions to the wheat proteins, egg white, veal, horse dandruff and feather proteins. We believe that with the wheat and egg proteins the child may have become sensitized passively, but in so far as wheat and egg were being consumed by her, such evidence is presumptive. However, with the veal protein we were absolutely assured by the mother that at the time of examination the child never had veal, and the only possible explanation for the potential hypersensitiveness to a protein of which the child had never partaken must be adduced from the fact that the sensitizing antibodies of veal were transferred passively in utero from the mother. We believe that the same situation obtains with the horse dandruff as compared to the mother's contact before marriage. With the feather proteins, as with the wheat and egg, the possibility of passive transfer plus reactivation

after birth must be considered feasible. For the entire Group I we have shown the presence of Prausnitz-Küstner specific antibodies to all of the substances in both the mother's and child No. 1 blood sera but not in the non-sensitive child's serum. So that we believe there is strong evidence for the assumption that sensitizing antibodies have been transferred from the mother to her child.

In Group II are certain sensitivities such as ragweed, cattle hair, dog hair, etc., in the mother and none in the child. With one of this group, namely dog hair, we showed the presence of Prausnitz-Küstner antibodies in the mother's blood but not in the child's blood. We believe that with these substances, for some unknown reason, the sensitization was not transferred or might have worn off because of its passive nature.

In Group III there is hypersensitiveness in the child No. 1 to such substances as peanuts, beef, cow's milk, extracts from the child's cottonseed mattress and feather pillow, chicken and certain vegetables. In explanation of this group several factors may play a rôle. The mother, during the pregnancy with this child, consumed one and a half quarts of milk a day and had a craving for peanuts. With peanut were shown the presence of Prausnitz-Küstner antibodies in the child's blood and not in that of the mother. It is highly probable that here is an active sensitization in utero, for the child had never indulged in peanuts. So, as with the veal, potential sensitization exists; passive in the former instance, and active in the latter. The sensitization to the feather pillow and cottonseed mattress was established through inhalation, and sensitization to the remaining foods in this group was induced through ingestion. No explanation at the present state of our knowledge can be offered for the high degree of susceptibility in one child and the complete absence of susceptibility in the second child. The question of susceptibility or receptivity to protein hypersensitiveness still remains the moot problem in hypersensitiveness.

Studies on Passive Transfer to Normal Guinea Pig and Normal Human Recipient.

During the course of these studies we gained consent of Mother S to subject herself to the experimental inhalation of horse dandruff in our laboratory (but did not have this same opportunity with the child). After two minutes of inhaling the dander dust she developed a very severe attack of asthma; she was given adrenalin twice after twenty minutes of observation.

Blood had been drawn from her about one month prior to this contact at the height of her asthmatic attack, and about two weeks later, and in Table II will be noted the instance of true anaphylactic passive sensitization of guinea pigs with human serum. This passive

transfer of human antibodies into the lower animals is consummated rarely but clearly links up the human allergic and the anaphylactic antibodies.[9]

TABLE II

GUINEA PIGS PASSIVELY SENSITIZED TO HORSE DANDER WITH SERUM OF MOTHER S, SHOWING IDENTITY OF ALLERGIC ANTIBODY AND ANAPHYLACTIC ANTIBODY

ANIMAL NO.	DATE	SENSITIZING DOSE OF HUMAN SERUM	INTERVAL OF DAYS	SHOCKING DOSE— DANDER EXT.	RESULTS
1878	12/ 9/29	1 c.c. Iv.	1	0.5 c.c. Iv.	++
1880	"	1 c.c. Iv.	1	0.5 c.c. Iv.	++++
1881	"	1 c.c. Iv.	1	0.5 c.c. Iv.	+
1892*	1/ 6/30	2 c.c. Ip.	2	0.25 c.c. Iv.	−
1893*	"	2 c.c. Ip.	2	0.25 c.c. Iv.	+++†
1894*	"	2 c.c. Ip.	2	0.5 c.c. Iv.	++
1895	1/15/30	4 c.c. Ip.	1	0.5 c.c. Iv.	+
1896	"	4 c.c. Ip.	1	0.5 c.c. Iv.	−
1897	"	2 c.c. Ip.	1	0.5 c.c. Iv.	−

Iv—intravenous
Ip—intraperitoneal

+ + + + — anaphylactic death
+ + + — marked anaphylaxis with recovery
+ + — moderate anaphylaxis with recovery
+ — suggestive anaphylaxis
− — negative anaphylaxis

*Animals 1892, 1893 and 1894 were injected with blood serum taken from patient at height of asthmatic attack induced by the inhalation of horse dandruff. Other groups were injected with blood serum collected before and after this exposure.

†Fig. 1, uterine strip, Dale experiments.

Fig. 1 is a positive Schultz-Dale tracing of animal 1893 (see Table II). This experiment including an intravenous injection and uterine strip, was done by a special method described in another paper.[10]

Passive transfer tests to the human subject were made according to the Prausnitz-Küstner method with the blood serum of Mother S on a normal recipient. Eight injections of 0.2 c.c. were given intracutaneously in the arm. The following day scratch tests gave positive reactions to wheat, egg white, whole egg, horse dander, veal and dog hair. The following day, a test for the passage of unchanged protein through the recipient's intestinal tract was made, the recipient taking four eggs on an empty stomach. A half hour later urticarial wheals appeared at the points of injections; they were large and persisted for one and a half hours. Of the areas tested with whole egg the preceding day, one area was apparently desensitized whereas another was not. Four hours later two eggs were ingested and no response occurred, indicating desensitization. The blood serum of child No. 1 was injected in another recipient in the same manner as with Mother S. Positive skin tests were obtained to wheat protein, egg, veal, horse dander and peanut. An intestinal absorption test was done with peanut and within a half hour a positive local passive transfer. As noted in Table I the antibodies of Group I were found in Mother S and Child No. 1. In Group II the antibodies of dog hair were found in Mother S and not in Child No. 1, and in Group III the antibodies of peanut were found in Child No. 1 and not in Mother S.

Table III represents a summary of the passively transferred antibodies.

TABLE III

ALLERGIC ANTIBODY PASSIVELY TRANSFERRED TO NORMAL SKIN AND TO GUINEA PIG

ANTIGEN	GROUP	MOTHER S	CHILD I	CHILD II
Veal		+	+	−
Horse dandruff*	I	+	+	−
Dog hair	II	+	−	−
Peanut	III	−	+	−

Antibody to horse dander of Mother S's serum passively sensitized guinea pig.

The passive transfer experiments therefore show that antibodies were present in Mother S's blood in high enough titer to pass into one of her children; in Group II the antibodies apparently were of low

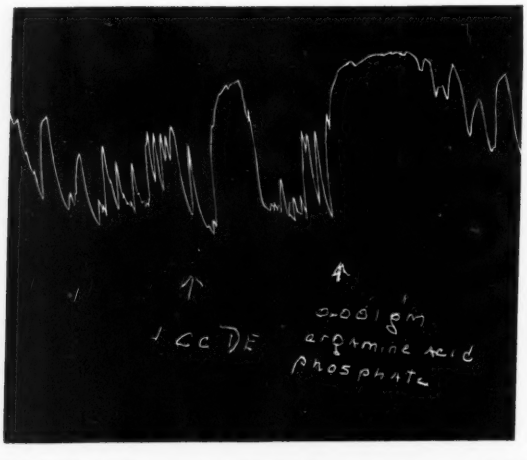
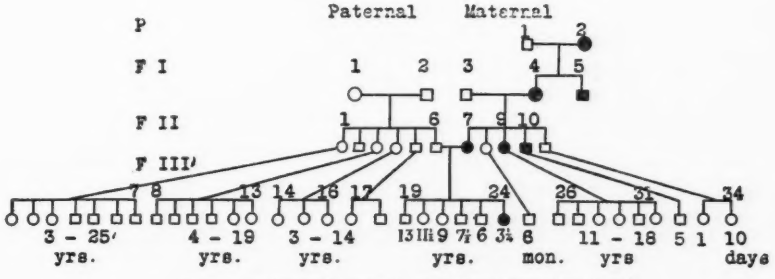


Fig. 1.—Sensitization of uterine strip with Mother S serum containing allergic antibodies to horse dander.

titer and did not pass through, or had worn off in the child; in Group III the absence of antibodies in the mother's blood and their presence in the child's blood indicate that the antibodies were actively established in the child in utero or after birth. The correlation of the horse dander antibodies passively transferred to a normal human recipient and to the guinea pigs links the identity of the allergic antibody and the anaphylactic antibody.[9]

Studies on Family W: General History.—The patient, a child of three years and three months of age, was referred to us suffering from severe eczema and asthma. Her first allergic manifestation came at about two months of age; it became progressively worse up to eight months of age and has persisted ever since as a definite eczema. Asthma began at about three years of age and the child has had recurrent attacks, having four attacks in the past three months. All attacks are typical

and usually last about forty-eight hours. History reveals certain dislikes to peaches and eggs; prior to and during her attacks the child has been eating wheat cereal twice a day. Mother W, the patient's mother, is thirty-one years of age and suffers from asthma and hay fever. She gives the following unusual history: During childhood she had asthma and then a complete period of remission up to six years ago. The interesting point is that this mother has six children and during the gestations of her first five children had been absolutely free of any allergic manifestations. But between the pregnancy of her fifth and sixth child, she developed asthma and hay fever. The hay fever is perennial and the asthmatic attacks have occurred frequently up to date. During the pregnancy with the last child, i.e., the patient noted above, she had hay fever and many severe attacks of asthma. During the antepartum period of the patient she ate ex-



P 2 - maternal great grandmother (asthma)
F I 4 - " grandmother (asthma)
F I 5 - " granduncle (asthma)
F II 9 - " aunt (asthma)
F II 10 - " uncle (asthma, hay fever)
F II 7 - mother W (asthma, hay fever)
F II 6 - father W (normal)
F III 24 - patient (asthma, eczema)

Chart 2.—Family W.

cessively of puffed rice, Uneeda biscuits, bread, and milk (two quarts a day). The mother and child were studied over a period of three years and the following is an analysis of the data obtained:

Hereditary Background.—Chart 2 gives a summary of the hereditary background. It is noted that in this family which is fairly large there appears to be a definite instance of allergy on the maternal side, having appeared for three generations, in a maternal uncle and in a maternal aunt and uncle. The paternal side is apparently all negative. There are a total of 52 members of which seven are allergic.

Skin and Allergic Clinical Tests.—The allergic skin tests were done on Mother W and her sensitive child No. 6. Curiously enough no positive skin reactions were ever obtained on Mother W, though she has been studied for three years. She was tested a number of times in the past year in innumerable areas of the body, this being done to

rule out any possible local skin refractoriness noted by Alexander and McConnell[11] and Ratner,[12] and she still remained a skin negative case. This test negative type of case is definitely accepted by various investigators such as Rackemann,[13] Rowe,[14] Ratner[12] and others. During the three years of study she was shown to be egg-sensitive by clinical test. When given an eggnog she developed a severe asthmatic attack which was unmistakable and was presented to a number of doctors at the hospital for clinical corroboration. The attacks thus induced were relieved by adrenalin. At one time the attack was so severe that she had to be given repeated injections of adrenalin and was ill all night. So that there is no question that clinically Mother W is an asthmatic, sensitive to egg (no other sensitivities were proved). Her hay fever was also a question of clinical observation and was never proved by skin test. With child No. 6 we did obtain positive reactions to egg white, ovo-mucoid, peach, ragweed, an extract of her feather pillow and suggestive reactions to wheat and feather proteins. The other five sibs were nonallergic and gave no reactions to any of the proteins to which they were tested.

Passive Transfer Tests.—Passive transfers were done with the bloods of both Mother W and Child No. 6; we were unable to find Prausnitz-Küstner antibodies. Two years later the following more elaborate tests of passive transfer were done: Sensitive child No. 6 was tested again and found to be sensitive to egg and the ragweeds. Blood was drawn and the serum injected intracutaneously into seven recipients. All passive transfers were negative to egg and ragweed. These seven recipients were given an intestinal absorption test (three tablespoonfuls of egg white) and none showed any positive absorption. Mother W was again tested in 44 different parts of the body with egg by scratch and intracutaneous tests, and none of the tests were positive. Blood was drawn and the serum injected into 23 recipients. All were tested against egg white and all tests were negative. These recipients were also given egg white by mouth and none showed any absorption reaction. The bloods of Mother W and sensitive child No. 6 were passively transferred to guinea pigs with negative results.

General Laboratory Tests.—Complete blood chemistry tests were done on Mother W, sensitive child No. 6 and five sibs. The blood chemistry tests were essentially normal except that in Mother W and Child No. 6 the plasma CO_2 was 72 and 76 volumes per cent respectively whereas the five nonallergic sibs ranged from 56 to 65 volumes per cent. The P_H in the two allergics was 7.36 and 7.37 respectively which were generally higher than the sibs who ranged between 7.27 and 7.32. The eosinophile studies showed a tendency to high eosinophilia both in the allergic mother and child and in the nonallergics

except that the eosinophiles ran up to 22 per cent in the allergic child and 16 per cent in the allergic mother, whereas the nonallergics did not run quite so high.

COMMENT

In this paper there is evidence to show that under certain conditions a highly sensitive allergic mother can sensitize the fetus in utero, but demonstration of this fact is difficult, for it does not occur with as great a regularity as under experimental conditions with the guinea pig. In Family S we showed the mother's and the child's bloods to contain identical circulating antibodies to certain antigens. The mother's blood, however, had antibodies to other substances not present in the child's blood, and the child's blood conversely contained antibodies of still other substances not present in the mother's blood. Thus we have a child who is sensitized congenitally by preformed antibodies and antigens from the mother's circulation, and further sensitized to other substances after birth through the respiratory and intestinal tracts.

The complexity and difficulty of demonstration of these factors are emphasized in Family W where Mother W who had no asthma during the period of gestation of her first five children developed asthma and hay fever after the birth of her fifth child and continued on until the birth of her sixth child. Mother and child were shown to be sensitive to egg proteins in common, and we presume that a passive congenital hypersensitiveness must have ensued in the case of the sixth child, but were unable to show the presence of Prausnitz-Küstner antibodies as was done with Family S.

In a recent study, Bell and Eriksson[15] found Prausnitz-Küstner antibodies in the sensitive mother's blood and not in the respective cord bloods of ten cases studied. This study tends to show that the antibodies are not always present in the infant's blood, and is very closely related to the evidence in Family S wherein we showed the presence of Prausnitz-Küstner antibodies in the mother and one child to only certain of her antibodies, and an entire absence of these antibodies in the second child. So what Bell and Eriksson found with the cord blood we were able to corroborate with the blood in later infancy. This transfer of sensitizing antibodies from the sensitive mother to her offspring therefore may or may not occur in every instance, for at the time of examination of a given specimen of blood the antibodies need not necessarily be present. This criterion obtains as well with passive experiments done on guinea pigs. Suffice it to say that we deem our evidence concrete enough to warrant the conclusion that antibodies may be transferred under certain conditions from a

sensitive mother to her offspring, and absence of evidence in other instances does not necessarily militate against the validity of such transfer being possible.

In six other families in which we studied the hypersensitivity of mother and child we found identical and nonidentical sensitivities to be present, but a recital of these cases would add nothing further to the protocols given above.

Certain salient factors have been demonstrated in congenital hypersensitiveness. The semipermeable placentas of certain animal species[16] permit the passage of sensitizing antibodies or antigens which results in a state of passive[5] or active[17] hypersensitiveness in the offspring. It is also shown that active sensitization thus established persists for a long period and may be carried over through two successive generations,[18] whereas passive hypersensitiveness is transitory and lasts for a comparatively short time. Further, antigenic substances inhaled by pregnant animals induces a state of respiratory anaphylaxis (asthma) and sensitizes the fetus in utero, for upon first contact with the inhalation of such dust, the newborn animal will manifest symptoms of respiratory anaphylaxis.[7]

We believe that congenital protein hypersensitiveness in its two phases, namely, that of active sensitization in utero and that of passive sensitization in utero, adds to the subject of protein hypersensitiveness a clearly defined mode or manner of inheritance which is not germinal or chromosomal, but which is the result of placental filtration. This manner of sensitization differs in no way from the sensitization which is acquired by individuals through the respiratory tract, intestinal tract or as a result of injection, but must be added to the accepted list of the foregoing modes of sensitization.

The presence of allergy on the maternal side as evidenced in the above cases is also emphasized by Bray[19] who found the presence of allergy on the maternal side more often than on the paternal. One might be led to conjecture that in such cases where the allergy preponderates on the maternal side that placental congenital transmission plays an important rôle.

The questions of scientific interest lie in the fact that the lower animal and the human being derive their sensitization through contact with antigen and antibodies which gain entrance into the blood stream through the various portals enumerated above. That an unknown quality of susceptibility must be there for the development of hypersensitiveness cannot be denied; the how and why of these conditions still remain moot.

No sharply defined lines can be drawn between human and animal hypersensitiveness, for circulating Prausnitz-Küstner antibodies which had been relegated solely to the human being and which were termed

"atopic reagins" are shown by our work to serve as anaphylactic antibodies, for passive transfer of these human antibodies produces anaphylactic sensitization in the guinea pig. Those investigators who advocate the theory of hereditary allergy seem to have left out of account the factor of congenital hypersensitiveness which so definitely occurs in the animal kingdom.

CONCLUSIONS

Identical protein hypersensitiveness may exist in the human mother and her child.

This hypersensitiveness is transferred via the placenta.

The allergic antibodies responsible for this sensitization of the fetus in utero are shown to have the qualities of the Prausnitz-Küstner antibodies, and are demonstrated both in the mother and her child.

These antibodies further are shown to be identical with the anaphylactic antibodies, for anaphylactic shock and sensitization of the uterus were produced in guinea pigs sensitized by human antibodies.

Congenital protein hypersensitiveness is divided into two phases, active and passive, the existence of which places this type of sensitization on a basis as clearly defined as sensitization acquired through other portals such as inhalation, ingestion or injection.

Since sensitization of a human being can be acquired in utero before birth, it follows that allergy is not always dependent on chromosomal inheritance.

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(For discussion, see page 209.)

HISTAMINE: THE REACTIVE SUBSTANCE IN HUMAN DANDER*

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FROM time to time, people have reported different substances which, when used for intradermal tests, would differentiate allergic from nonallergic individuals. Van Leeuwen working with human dander reported a substance which he claimed could be used in such an application. This is an extractable substance in the dander.

It was demonstrated by Van Leeuwen that with properly extracted human dandruff all allergics when tested intradermally gave positive skin reactions, whereas normal or nonallergic individuals so tested, with very few exceptions, showed no reactions. It is estimated by him that positive reactions were elicited in 90 to 95 per cent of allergics and were never demonstrable in so-called normals. We have prepared extracts according to Van Leeuwen and Van Niekerk,[1] by extracting human hair containing dandruff or hair and scrapings from arms and legs of individuals free from skin diseases. These extracts are prepared as strongly as possible with physiologic salt solution containing 0.5 per cent phenol as the extracting fluid. Extraction is carried out for two hours at room temperature, filtered through a Berkfeld filter, and tested for sterility. The test is made by injecting 0.1 c.c. intracutaneously into the forearm. Van Leeuwen and Van Niekerk supply proof that impurities such as house dust or bacteria present with the dander are not the cause of the reactions.

Feinberg, Taub and Unger[2] confirmed these findings in a series of 20 cases. Peshkin[3] has not been able to confirm them even when using extracts obtained from the original observers. In checking the technic and the work as outlined, we have felt that the substance giving the reaction was one of the proteolytic decomposition products of the dander or epithelium extracted. Hydrolysis of human dander with either steam, moderately weak acid or alkali gives off a typical amine odor. Human hair contains amino nitrogen in various combinations and has been found to be particularly rich in the amino acid cystine. Decomposition of human hair by hydrolysis has given a yield of as much as 13.92 per cent of pure cystine (Hawk[4]). It also contains other combinations of amino acids, one of them being histadine, the precursor of histamine which is derived from it. Both are extractable in weak caustic soda.

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In Van Leeuwen's work, the experiments were extended to include the layers of the skin other than the topmost one, and it was found that the external layer was the only one which contained the extractable substance, responsible for this typically differentiating skin reaction in allergic individuals. This is the layer which on the scalp, with dirt and secretions, forms dandruff. Hydrolysis of this same layer from the hairless portions of the body gives off amino nitrogen with the same typical amine odor but which apparently contains no sulphur and is not cystine. A solution of the hydrolyzed dander gives a physiologic reaction, which is typical, and identical with the contractions of the involuntary muscle of the guinea pig uterus given by dilute solutions of histamine hydrochloride.

Kymograph tracings were made to determine the effect of the hydrolyzed dander on the blood pressure of cats, and the physiologic reaction of this hydrolyzed dander was compared with the physiologic action of other similar and related substances on the blood pressure. The following substances were tested in this manner: (a) histamine,

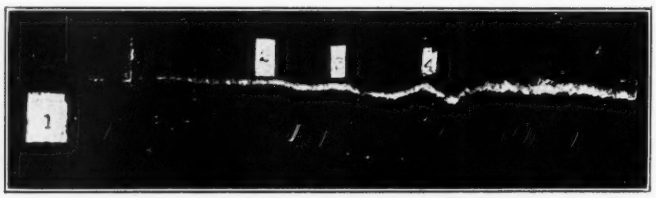

Fig. 1.—Kymograph tracing blood pressure of Cat.
(1) Adrenalin given intramuscularly 5 mm. 1 to 1,000.
(2) Cystine given intramuscularly 10 mm. 1 to 1,000.
(3) Human dander extract given intramuscularly 10 mm. 1 to 1,000.
(4) Histamine given intramuscularly 10 mm. 1 to 1,000.

chemically pure, dilutions 1 to 1,000 and 1 to 10,000; (b) cystine hydrochloride, dilution 1 to 1,000; (c) human dander (hydrolyzed), dilution 1 to 1,000 and 1 to 100.

In order to determine whether or not the physiologic results would check with the clinical ones, patients were tested with different solutions of histamine and human dander in normal salt solution. It was thought advisable to determine the effect by the scratch method, and 50 allergic patients in the desensitization clinic were chosen. These patients had all given positive reactions to some protein previously; all have given three-plus reactions or greater to one or more of the proteins tested by the scratch method. Usually one was selected who responded to either the pollens or the animal emanations. Reactions with this method were not definite and offered too many obstacles, so that it was discontinued in favor of the intradermal method.

Two facts were noted particularly: (1) the comparison between reactions of the allergic group and the nonallergic group; the

TABLE I

SKIN REACTIONS WITH HISTAMINE AND HUMAN DANDER ON 50 ALLERGIC PATIENTS AND ON 50 CONTROLS

DILUTION	NUMBER TESTED		TYPE OF REACTION	PERCENTAGE OF REACTIONS IN ALLERGICS		PERCENTAGE IN 50 NON-ALLERGIC CONTROLS	
	HISTAMINE	DANDER		HISTAMINE	DANDER	HISTAMINE	DANDER
1 to 10 thousand	10	6	5 plus	20	12	10	8
	15	19	4 plus	30	38	38	12
	17	15	3 plus	34	30	10	10
	8	10	2 plus	16	20	12	20
	0	0	1 plus	0	0	22	30
	0	0	negative	0	0	8	20
1 to 100 thousand	3	1	5 plus	6	2	0	4
	2	2	4 plus	4	4	32	30
	10	8	3 plus	20	16	2	4
	11	10	2 plus	22	20	16	12
	20	19	1 plus	40	38	20	16
	4	10	Pl. Min.	8	20	0	20
	0	0	negative	0	0	30	14
1 to 1 million	0	0	5 plus	0	0	0	0
	0	0	4 plus	0	0	0	0
	11	10	3 plus	22	20	24	20
	11	10	2 plus	22	20	12	10
	10	12	1 plus	20	24	10	12
	18	18	negative	36	36	54	56
1 to 10 million	0	0	5 plus	0	0	0	0 *
	0	0	4 plus	0	0	0	0 *
	0	0	3 plus	0	0	0	0 *
	0	0	2 plus	0	0	0	0 *
	5	3	1 plus	20	12	0	0 *
	4	4	Pl. Min.	16	16	20	12 *
	16	18	negative	64	72	80	88 *
1 to 100 million	4	2	Pl. Min.	16	8	All negative*	
	21	23	negative	84	92		
1 to 200 million	All negative					All negative*	

*Twenty-five patients tested only.

latter group was made up of patients in the wards of the hospital, fracture cases and convalescents. (2) The vanishing point of the reaction, i.e., the dilution at which the majority of each group gave the minimum or negative reaction. All individuals tested, allergic and nonallergic, gave a markedly positive skin reaction of two plus or more to a dilution of 1 to 1,000 of chemically pure histamine. This is due to the toxicity of the substance. Therefore, we chose as a starting point dilutions of histamine and dander of 1 to 10,000 each. Table I shows the results of the tests.

TABLE II

COMPARATIVE REACTIONS OF HISTAMINE AND HUMAN DANDER SOLUTIONS

50 PATIENTS ALLERGICS				50 PATIENTS NONALLERGICS	
DILUTION	HISTAMINE	DANDER		HISTAMINE	DANDER
1-10,000	17	15	3-Plus Reactions	5	5
1-100 million	10	8		1	2
1- 1 million	11	10		12	10
1- 10 million	0	0		0	0
1-10,000	0	0	Negative	4	10
1-100 million	0	0		15	7
1- 1 million	18	18		27	28
1- 10 million	16	18		40	22
1-100 million	21	23*		25	25
1-200 million	25	25*		25	25

*Only 25 patients of this dilution were tested for each.

DISCUSSION

The major premise is supported to a degree seen in Table I, namely that allergic individuals react to human dander extracts and to histamine in solution, more intensely than do nonallergic individuals. For example, in a dilution of 1 to 1,000 of either solution more than 80 per cent of allergic individuals give a three-plus reaction or greater, while of the nonallergic group, only 55 per cent give the same intensity of reaction. There is some varying degree of reactivity until the vanishing point is reached which occurs sooner in the nonallergic than in the allergic group. In a dilution of 1 to 1,000,000 the equality of reaction seems to occur, although more nonallergics give minor or negative reactions than do the allergics. In a dilution of 1 to 10,000,000 the allergic group still shows approximately 20 per cent reactivity while the nonallergic group is negative throughout.

It is interesting to note that the reactions in all dilutions for both the histamine and the dander extract are almost identical and that the percentages in each dilution for the series are in agreement. These two sets of tests were run at different times throughout the year and were observed by several sets of observers in the various clinics at our disposal. While the differentiating value of the extractable sub-

stance is only moderate and not definite enough to be used clinically, we were interested to find the results were as closely allied as shown, and that the substance extracted was this histamine or histamine-like material.

To check the substance extracted from dander chemically, the technic of Zimmerman,[5] was followed. This is for the colorimetric detection of histamine in solution, the reagents being the same as the diazo-sulphanilic acid-cobalt nitrate test. The violet coloration which is produced in pure solutions of histamine was precipitated out as a violet precipitate. This is a specific color reaction for histamine.

SUMMARY

1. Amino acids are produced in the hydrolysis of human dander among which are: cystine, histamine and histadine.

2. Physiologically the extractable substance in human dander is the same as dilute solutions of histamine.

3. Fifty patients were tested intradermally with solutions of different strengths of histamine and human dander extracts and the skin tests elicited were in agreement.

4. Chemically, the extractable substance in human dander gives, after the technic of Zimmerman, a color which is considered as being the specific color reaction for histamine.

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(For discussion, see page 214.)

A STUDY OF THE APPARENT ATOPIC SIMILARITY OF CERTAIN CHENOPODIALES POLLENS

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TWO families of the order *Chenopodiales* contain members which are frequently incriminated as causes of hay fever in the southwestern United States. Of the family *Chenopodiaceae,* three genera are important from this standpoint: *Chenopodium, Atriplex,* and *Salsola. Chenopodium album* (lamb's-quarters) and *Salsola pestifer* (Russian thistle) are two common species encountered locally. The family *Amaranthaceae* contain, among others, the genus *Amaranthus* with three local species, *Amaranthus spinosus* (spiny amaranth), *Amaranthus retroflexus* (red root pigweed), and *Amaranthus Palmeri* (careless weed); and the genus *Acnida,* a species of which, *Acnida tamariscina* (western water hemp), grows locally. The pollens of the above mentioned species, *Chenopodium album, Salsola pestifer, Amaranthus spinosus, Amaranthus Palmeri, Amaranthus retroflexus,* and *Acnida tamariscina,* all being found in this section, have been routinely used by us in preparing extracts for testing of hay fever patients for several seasons. These *Chenopodiales* pollens are, in our experience, the most common causes of summer and fall hay fever; ragweeds, so important elsewhere, are relatively unimportant offenders in this immediate locality (midwest Texas).

During the past season (1930) it was observed by us that patients giving a positive skin reaction to any one of the above mentioned species, gave, with few exceptions, positive reactions to all of the others. A similar observation has been made by Lamson[1] in a study of a large group of patients in Southern California. The high percentage of positive reactions to nearly all members of the group, in *Chenopodiales*-sensitive individuals, led us to study the group as a whole. The possibility of a close atopic relationship of the six species studied is obvious from the results of skin tests in the following series, admittedly small.

Private patients tested during the past year (1930-31) include 36 cases of this type. Patients tested prior to this time are not included because our records of such past cases show a considerable number of patients who were not tested with extracts of all six species. Testing was done by the scratch method with the exception of a few tests made intradermally for corroboration. Glycerin-saline extracts, personally prepared, were used in testing, 1 gm. of dry pollen being extracted with 100 c.c. of fluid. In this series of 36 cases, definite positive reac-

tions were obtained to all of the following species: *Amaranthus retroflexus, Amaranthus spinosus, Amaranthus Palmeri,* and *Acnida tamariscina,* with the exception of one individual who reacted only weakly to *Amaranthus Palmeri* and *Amaranthus retroflexus.* Sixty-nine and one-half per cent of the group gave strongly positive reactions to *Chenopodium album* and 80 per cent to *Salsola pestifer.* In no instance was a positive reaction obtained to *Chenopodium album* or *Salsola pestifer* without an accompanying positive reaction to the other species mentioned. In reviewing these cases, two patients treated in 1930 showed absence of reactions to one or more of the pollens studied, namely, *Amaranthus retroflexus* and *Chenopodium album* in one patient, and *Acnida tamariscina* and *Chenopodium album* in another. Upon retesting recently, to clarify this discrepancy, both of these patients showed definitely positive reactions to the pollen extracts found negative in 1930. The negative tests obtained in 1930 were probably in error. We consider that any series of patients routinely tested may show similar necessary corrections if retested.

TABLE I

THIRTY-SIX CASES TESTED IN 1930-31 WITH EXTRACTS OF SIX SPECIES OF *Chenopodiales Genera*

	MARKED OR MODERATELY POSITIVE	WEAKLY POSITIVE	NEGATIVE
Amaranthus spinosus	36	0	0
Amaranthus Palmeri	35	1	0
Amaranthus retroflexus	35	1	0
Acnida tamariscina	36	0	0
Chenopodium album	25	8	3
Salsola pestifer	29	6	1

The phenomenon of local passive transfer noted by Prausnitz and Küstner has been applied by Coca and Grove[2] in determining the identity or nonidentity of atopens of different origin. Serum of a sensitive individual when injected intradermally into the skin of a normal individual sensitizes for an indefinite period this skin at the injection site. This site when tested gives positive reactions for all atopens to which the person whose serum was used reacts. Moreover, these sites may be desensitized or exhausted of their reacting ability by repeated injections of a given atopen. This exhaustion, however, is specific for this particular atopen so that when a nonrelated atopen is injected a reaction again occurs. This would not be true were the atopens identical. This method has been used by Spain and Hopkins[3] in demonstrating the identity of ragweed atopens. The same method was used by us in studying the pollens of this group. That this method alone may be accepted as sufficient proof of the atopic identity of pollens of different origin is questioned by Piness and Miller[4] whose experiments

TABLE II

DESENSITIZATION OF SITES PASSIVELY SENSITIZED WITH SERUM OF PATIENT SENSITIVE TO SIX SPECIES STUDIED. PATIENT ALSO SENSITIVE TO *Juniperus Mexicana* (MOUNTAIN CEDAR)

ROW 1					ROW 2					ROW 3					ROW 4					ROW 5					ROW 6				
SENSITIZED 4-30-31					SENSITIZED 4-30-31					SENSITIZED 4-30-31					SENSITIZED 4-30-31					SENSITIZED 4-30-31					SENSITIZED 4-30-31				
5-1	5-2	5-3	5-4	5-5	5-1	5-2	5-3	5-4	5-5	5-1	5-2	5-3	5-4	5-5	5-1	5-2	5-3	5-4	5-5	5-1	5-2	5-3	5-4	5-5	5-1	5-2	5-3	5-4	5-5
A.S.	A.S.	A.S.	A.P.	J.M.	A.P.	A.P.	A.P.	A.S.	J.M.	A.R.	A.R.	A.R.	A.S.	J.M.	A.T.	A.T.	A.T.	A.S.	J.M.	C.A.	C.A.	C.A.	A.S.	J.M.	S.P.	S.P.	S.P.	A.S.	J.M.
++	++	0	0	++	++	++	0	0	++	++	+	0	0	++	++	+	0	0	++	++	+	0	++	++	++	+	0	++	++
			A.R.					A.R.					A.P.					A.P.						A.P.					A.P.	
++	++	0	0		++	++	0	0		++	+	0	0		++	+	0	0		++	+	0	++		++	+	0	++	
			A.T.					A.T.					A.T.					A.R.						A.R.					A.R.	
++	++	0	0		++	++	0	0		++	+	0	0		++	+	0	0		++	+	0	++		++	+	0	++	
			C.A.					C.A.					C.A.					C.A.						A.T.					A.T.	
++	++	0	0		++	++	0	0		++	+	0	0		++	+	0	0		++	+	0	++		++	+	0	++	
			S.P.					S.P.					S.P.					S.P.						S.P.					C.A.	
++	++	0	0		++	++	0	0		++	+	0	0		++	+	0	0		++	+	0	+−		++	+	0	0	

A.S. Injection of *Amaranthus spinosus* into passively sensitized area.
A.P. Injection of *Amaranthus Palmeri* into passively sensitized area.
J.M. Injection of *Juniperus Mexicana* into passively sensitized area.
A.R. Injection of *Amaranthus retroflexus* into passively sensitized area.
A.T. Injection of *Amaranthus tamariscina* into passively sensitized area.
C.A. Injection of *Chenopodium album* into passively sensitized area.
S.P. Injection of *Salsola pestifer* into passively sensitized area.
++ is marked or moderately positive reaction.
+ is weakly positive reaction.
+− is questionable reaction.
0 is negative reaction.

with pollens of the family *Graminaceae* led to contradictory conclusions. Black's hypothesis[5] that the atopic reagin may be an antibody reacting with some fraction of pollen other than the true atopen of clinical hypersensitiveness, if proved, would lessen materially the practical application of such experiments. Conclusions, however, drawn from this procedure as at least supporting evidence, are certainly worthy of consideration.

The sera of nine individuals in our series were studied. The following technic was used: Blood was drawn from a patient sensitive to all pollens under question; the serum separated under sterile conditions and run through a Seitz filter. This was kept in the ice box until ready for use. Six rows of five sites each, in the skin of a non-sensitive individual, were sensitized with this serum, 0.05 c.c. of serum being injected into each site. The arm and forearm were used chiefly in these experiments, although the back, abdomen, and thigh were also used. Each row of sites was desensitized to different extracts according to Table II.

After desensitization, the five sites were retested to the other members of the group. Later these sites were retested to an unrelated pollen, to which the individual whose serum was used was also sensitive. Extracts used in desensitization and testing of desensitized sites were prepared by Coca's technic,[6] and diluted so that each cubic centimeter represented 0.1 mg. of N. Five one-hundredths c.c. was used at each injection (0.005 mg. N). Experiments were conducted on two individuals with each serum. In the large number of sites tested, only a few discrepancies occurred which required repeating. Three of the patients whose sera were studied were sensitive to only the six species, and hence no adequate control of a nonrelated pollen was available.

On one occasion two different groups of sites were sensitized with two sera at the same time. The locations used were the right and left thighs. On injection of one group of sites on the following day, strongly positive reactions occurred at all sites on the other. These reactions required thirty minutes or longer to develop and persisted for forty-eight hours, although the reactions of the injected sites appeared promptly and subsided within a few hours. The second group of sites was left undisturbed until the experiment in the first group was completed. Subsequent injections of this second group gave strongly positive reactions. Apparently the first reactions effected by blood stream transmission of the atopens conferred very little desensitization.

The results of the experiments may be summarized as follows: Sites desensitized to *Amaranthus spinosus* gave negative reactions on retesting with other members of the group, although questionable reactions were obtained in four instances which necessitated repeating. The test repeated, gave negative reactions in each instance. Briefly, the

same results were obtained in sites desensitized to *Amaranthus Palmeri, Amaranthus retroflexus,* and *Acnida tamariscina.* Sites desensitized to *Chenopodium album* and retested to *Salsola pestifer* gave negative reactions in approximately 50 per cent of the experiments. Sites desensitized to *Salsola pestifer* and retested to *Chenopodium album* gave negative reactions in approximately 75 per cent of the experiments. A typical experiment is shown in Table II. Sites desensitized to extracts of each of the six species gave the expected strongly positive reaction to an unrelated pollen extract in those sera used from patients also reacting to an unrelated pollen.

The method of Walzer and Bowman[7] based upon the finding that mixtures of serum and atopen are neutralized on incubation in vitro,[2] was utilized in two experiments. Although the results were identical to those of the other experiments in regard to success or failure of desensitization upon retesting, marked and prolonged reactions occurred upon injection of the mixture before retesting. The mixtures were incubated six hours before injection. Our unfamiliarity with this method led us to discard it. Our first impression was that at least a part of the neutralization occurred in vivo.

Deductions made from these experiments were that sites desensitized to any one of the species of the family *Amaranthaceae* studied become desensitized to the other species of the family. Moreover, sites desensitized to any one species of the above family become desensitized to *Chenopodium album* and *Salsola pestifer.* However, desensitization of the sites to the latter two species does not desensitize to the four species of *Amaranthaceae.* Desensitization of sites to *Salsola pestifer* does not always desensitize to *Chenopodium album* (75 per cent in our experiments) and conversely even to a lesser degree (50 per cent).

A fourth point of evidence used by others in establishing the identity of atopens of different origin is based upon the substitution during treatment of maximum tolerance injections of one atopen for another without constitutional reaction, has not been completely established by us. However, substitution of injections of relatively high concentration built up during this seasons's treatment, has been performed without untoward effects in a number of instances. We are now treating our *Chenopodiales*-sensitive patients with single extracts of pollens of the *Amaranthaceae* group, certain patients receiving only one extract. The relative success of treatment of the individual patients will be observed later in the season.

A knowledge of the relationship of the atopens of this group has many obvious advantages. Our studies suggest that only one of the members of the family *Amaranthaceae* need be used either for testing or for treatment of patients sensitive to the six species studied. The possibility that this may hold true for other species under the order *Chenopodiales* is enticing but beyond the range of these observations.

Treatment instituted conjointly with identical atopens may conceivably lead to frequent constitutional reactions because of massive dosage.

SUMMARY

1. The botanical classification of six species under the order *Chenopodiales* commonly found in this section is reviewed.

2. In a series of 36 patients tested during the past year, it was observed that reactions to one member of the *Chenopodiales* group was accompanied with reactions to all other members of the group with few exceptions, and a close relationship of these atopens was thereby suggested.

3. By the method of passive transfer, further corroboration of this apparent atopic similarity was established. Our experiments indicate that all atopens of the six species studied are contained in the pollens of *Amaranthus spinosus, Amaranthus Palmeri, Amaranthus retroflexus,* and *Acnida tamariscina,* but all of the atopens are not contained in the pollens of *Salsola pestifer* or *Chenopodium album.*

4. From this study it is suggested that only one of the members of the family *Amaranthaceae* studied need be used either in testing or in treatment of patients sensitive to any one or all of the six species studied.

5. Should these observations be substantiated, treatment of *Chenopodiales* sensitive patients would become greatly simplified.

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THE INCIDENCE AND RÔLE OF PARANASAL SINUS DISEASE IN HAY FEVER*†

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THE present report deals with a phase of the studies being conducted in our clinic on the rôle of paranasal sinus disease in bronchial asthma. It seemed to us that bronchial asthma as occurring in hay fever patients presented a smaller number of uncontrolled variables and complicating factors, the evaluation of which might prove difficult in the interpretation of findings and results.

We have therefore made observations on 75 hay fever patients seen in the Allergy Section of the Hospital of the University of Pennsylvania. In each instance in addition to a careful history and skin tests both with pollens and the commoner inhaled allergens, there was carried out a thorough clinical examination of the nose and paranasal sinuses. In 55 of the 75 patients there was also made a roentgen-ray examination of the sinuses. Both the clinical and the roentgen-ray examiner rendered independent opinions, since neither was informed of the other's findings. The details of the clinical examination and roentgen-ray technic have been described elsewhere.[1]

All examinations were made before the hay fever season, when the patients were still symptom-free. In no instance was the routine roentgen-ray examination supplemented by the injection into the sinuses of radio-opaque substances, such as lipiodol.

The cases fall naturally into three groups: first, those with simple uncomplicated hay fever; second, those with asthma during the pollen season; third, those who in addition to hay fever and seasonal asthma suffer from asthma at other times of the year. However, no patients were included in the last group who had had asthma previous to their pollen disease. In other words, pollen hypersensitiveness was in each instance the first manifestation of respiratory allergy.

In Table I are summarized the roentgen-ray findings in the 55 patients so studied. Somewhat to our surprise, there was found a greater percentage of positive findings in patients with uncomplicated hay fever than in the cases with seasonal and perennial asthma. On the other hand, the degree of sinus involvement shown by the average patient;

*From the Allergy Section of the Medical Clinic of the Hospital of the University of Pennsylvania.

†Read before the Association for the Study of Allergy, Philadelphia, June 9, 1931.

that is, the number of sinuses involved per patient was distinctly greater in those patients with both seasonal and perennial asthma in addition to their hay fever than in those with uncomplicated hay fever or with only seasonal asthma and hay fever. In fact, as will later appear, the nasal findings in these latter groups of patients are more nearly normal than in the average population in this vicinity.

TABLE I

ROENTGEN-RAY FINDINGS

DIAGNOSIS	TOTAL NO. OF CASES	POSITIVE FINDINGS			NEGATIVE FINDINGS	
		NO. OF CASES	PER CENT	DEGREE*	NO. OF CASES	PER CENT
Hay fever	20	17	85	2.4	3	15
Hay fever and seasonal asthma	19	12	63.7	2.0	7	36.3
Hay fever, seasonal and perennial asthma	16	13	81.2	3.0	3	18.4

*Figures in this column represent the average number of sinuses involved per patient: counting each sinus or sinus group as 1, then a pansinusitis would be expressed by 8; involvement of the ethmoids on both sides by 2, etc.

In Table II are summarized the clinical findings in the 75 patients so examined. Here both the percentage of patients with sinus disease and the sinus involvement per patient are lower in the uncomplicated hay fever patients, more marked in patients with hay fever and seasonal asthma, and greatest in patients with seasonal and perennial asthma in addition to their hay fever. The trend of the figures for sinus involvement per patient is the same for both clinical and roentgen-ray examinations. The fact that in the uncomplicated hay fever group fewer patients were found who had sinus abnormality on clinical examination than on roentgen ray may be accounted for in several ways. The chief reason is that in the case of ethmoid and sphenoid disease the absence of pus in the nose may mislead the clinical examiner into a negative diagnosis. Then, too, positive roentgen-ray findings may

TABLE II

CLINICAL FINDINGS

DIAGNOSIS	TOTAL NO. OF CASES	POSITIVE FINDINGS			NEGATIVE FINDINGS	
		NO. OF CASES	PER CENT	DEGREE*	NO. OF CASES	PER CENT
Hay fever	28	15	53.6	2.3	13	46.4
Hay fever and seasonal asthma	29	18	62	3.6	11	38
Hay fever seasonal and perennial asthma	18	12	66.7	4.0	6	33.3

*See Table I.

be due to disease which occurred in the past and is now no longer active. In the presence of asthma it is also possible that the clinical examiner is more likely to suspect sinus disease.

The question of the relative efficiency of the clinical and roentgenologic methods of examination for sinus disease has been extensively discussed elsewhere[1] and will therefore not be considered at this time. It may be of interest, however, to note the discrepancies in the results of these examinations as set forth in Table III. When the two examiners disagree, it is usually because the clinician fails to recognize abnormalities which the roentgenologist discovers. The table fails to show the full extent of the discrepancies of the two examinations, in that it does not give the findings for the individual sinuses.

We cannot help but stress at this time the importance of the complete independence of these two methods of examination. Neither the roentgenologist nor the rhinologist should know of the other's findings at the time of the first examination. Quite aside from any undue in-

TABLE III

COMPARISON OF CLINICAL AND ROENTGEN-RAY FINDINGS

DIAGNOSIS	TOTAL NO. OF CASES	AGREEMENT (COMPLETE OR PARTIAL)		DISAGREEMENT	
		CLINICAL + X-RAY +	CLINICAL 0 X-RAY 0	CLINICAL 0 X-RAY +	CLINICAL + X-RAY 0
Hay fever	20	13	3	4	0
Hay fever and seasonal asthma	19	10	4	2	3
Hay fever, seasonal and perennial asthma	16	9	2	4	1

fluence which one examiner can have upon the other, notably the roentgenologist upon the rhinologist, a comparison of their independent reports gives a much better idea of the degree of involvement, severity and activity of the sinus disease in question. Subsequent comparisons and check-ups are of course in order and often yield additional information, as well as improve the examiners' skill and judgment.

Figures for incidence of sinus disease in hay fever or asthma have no absolute value unless they are compared with similar figures obtained in a group of normal controls. Furthermore, each set of figures must be obtained in groups of persons from the same geographic region, for the incidence of sinus disease varies widely with locality. In 1929, Kern and Schenck[1] reported from this clinic on sinus studies in 200 asthmatic patients and in 50 so-called "normal" controls. The control group included persons who gave no history of recent respiratory disease, no history of susceptibility to colds, no history of frank sinus disease in the past and whose ages fell proportionately into the same decades as those of the 200 asthmatic patients. A group so se-

lected may well be considered as less likely to show sinus abnormality than any average group of 50 persons.

In Table IV the roentgen-ray findings in these various groups are compared. Three points seem worthy of emphasis: 1, there is a high incidence of sinus abnormality in so-called "normals" in this vicinity, so that by comparison the high figures for sinus abnormality in bronchial asthma are not nearly so impressive as when considered alone; 2, if we group the 39 patients with hay fever and seasonal asthma, the number of patients with sinus involvement in this group is hardly greater than in the so-called normal persons and the number of sinuses involved per patient in the hay fever group is distinctly less than in the controls; 3, the percentage of sinus abnormality in the hay fever patients with both seasonal and perennial asthma is practically the same as in the group of 200 asthmatic patients, but the number of sinuses involved per patient is decidedly less, and even less than in

TABLE IV

COMPARISON OF ROENTGEN-RAY FINDINGS IN HAY FEVER PATIENTS WITH THOSE IN ASTHMATIC PATIENTS AND "NORMALS"

DIAGNOSIS	TOTAL NO. OF CASES	POSITIVE X-RAY FINDINGS		NUMBER AFFECTED SINUSES PER PATIENT
		NO. OF CASES	PER CENT	
Hay fever alone and hay fever with seasonal asthma	39	29	74.4	2.2
"Normals"	50	36	72	3.9
Hay fever with seasonal and perennial asthma	16	13	81.2	3.0
Bronchial asthma	200	171	80.5	4.14

the "normal" controls. We therefore feel justified in saying that the average hay fever patient's nose is more nearly normal than in our average population.

Table V gives the figures for other intranasal abnormalities found, including the presence of septum-turbinate contact or polyps or of both. Septum-turbinate contact was recorded as present if the contact persisted after moderate shrinking of the mucosa with cocaine or adrenalin. It is perhaps significant that no patient in the uncomplicated hay fever group had both polyps and septum-turbinate contact and that the percentage of patients with both seasonal and perennial asthma showing these abnormalities is quite high. Another noteworthy point is this: of 24 patients with contact or polyps or both who had roentgen-ray examinations, 19 showed evidence of sinus involvement, with an average of 4.4 sinuses per patient.

The finding of a higher percentage of sinus disease and other nasal abnormalities in those hay fever patients with seasonal and perennial asthma might be interpreted by some as evidence that these sinus and intranasal abnormalities are the cause of the complicating asthma.

Particularly the rhinologists have argued on such evidence. Some have even gone so far as to claim that the nasal abnormalities are the chief factor in the etiology of hay fever! For example, only three years ago Carmody and Greene[2] wrote that "without infection in the sinuses or without pathological mucous membranes, irritants, such as dust, pollens, bacteria, foods, and emanations of all sorts do not produce allergic coryza or hay fever." But there is further evidence to be considered.

TABLE V

OTHER INTRANASAL ABNORMALITIES

DIAGNOSIS	TOTAL CASES	NO. WITH SEP. TURB. CONTACT	NO. WITH POLYPS	NO. WITH BOTH CONTACT AND POLYPS	TOTAL NO. WITH SOME ABNORMALITY	PER CENT WITH SOME ABNORMALITY
Hay fever	28	7	2	0	9	32
Hay fever and seasonal asthma	29	6	3	2	11	38
Hay fever seasonal and perennial asthma	18	3	3	4	10	55

In Table VI are presented in summary the results of skin tests in the 67 patients who were tested both with pollens and the commoner inhaled allergens: chicken feather, goose feather, cat hair, dog hair, sheep wool, cotton seed, orris root, kapok, house dust. Tests were made by the cutaneous method. All patients reacted to pollens with the exception of one who nevertheless gave a typical history of a seasonal hay fever with attendant asthma. Less than half of the hay fever group reacted to substances other than pollens. Nearly three-fourths of those with a complicating seasonal asthma reacted to other inhalants and all but one of the patients with perennial and seasonal asthma were found sensitive to substances other than pollens. These figures are certainly more impressive than those for sinus disease in these various groups and could be made even more so if we set beside them the low figures for positive skin reactions which have been found in normal controls.

TABLE VI

RESULTS OF SKIN TESTS

DIAGNOSIS	TOTAL CASES	POLLEN REACTIONS	ONLY POLLEN REACTIONS	REACTIONS TO OTHER INHALANTS		
				NO. OF CASES	PER CENT	AVE. NO. REACTION PER PATIENT
Hay fever	25	25	15	12	44	2.9
Hay fever, seasonal asthma	25	24	7	18	72	2.3
Hay fever, seasonal and perennial asthma	17	17	1	16	94	3.3

There is still further evidence to be advanced, as furnished by the data on the results of treatment as shown in Table VII.

TABLE VII

RESULTS OF TREATMENT*

DIAGNOSIS	RESULT	SINUSES NEG. OTHER ABNORMALITIES NEG.	SINUSES NEG. OTHER ABNORMALITIES POS.	SINUSES POS. OTHER ABNORMALITIES NEG.	SINUSES POS. OTHER ABNORMALITIES NEG.
Hay fever (18 cases)	Good	5 cases	—	7 cases	3 cases
	Slight	1 "	—	0 "	1 "
	Failed	0 "	—	1 "	0 "
Hay fever, seasonal asthma (17 cases)	Good	2 "	3 cases	5 "	2 "
	Slight	1 "	0 "	1 "	0 "
	Failed	1 "	0 "	1 "	1 "*
Hay fever seasonal and perennial asthma (9 cases)	Good	1 "	1 "*	4 "	1 "
	Slight	0 "	0 "	1 "	1 "
	Failed	0 "	0 "	0 "	0 "

*These two patients were the only ones who had surgical treatment in addition to specific therapy: in one instance, a submucous resection, and in the other, a submucous resection and a right ethmoid exenteration.

Forty-four patients of this series received treatment at our hands. In every instance this consisted in the prophylactic and phylactic injection of pollen extract, the avoidance of other inhalant allergens to which the patient reacted, and, in a few instances, the injection of house dust extract. In addition to this specific treatment, only 2 patients were subjected to nasal surgery; the rest received no local treatment for any intranasal disease. It would seem that the presence or absence of sinus disease had no effect on the results of treatment.

In order to make this clearer we have further analyzed these figures in Table VIII.

TABLE VIII

RESULTS OF SPECIFIC TREATMENT IN UNOPERATED PATIENTS

RESULTS	GOOD	SLIGHT	FAILURE
All cases with sinuses +	23	3	2
All cases with sinuses 0	11	2	1
Hay fever only	15	2	1
Hay fever and asthma	18	4	2

Here are given the results of specific treatment in the 42 patients who had no nasal operations. In the upper half of the table we grouped all the patients with sinus disease, irrespective of whether they had hay fever or hay fever and asthma, and all the patients with normal sinuses irrespective of whether they had hay fever or hay fever and asthma. It will be seen that the results are practically the same in the two groups, if anything a bare trifle better in the patients with abnormal sinuses than in those with normal sinuses. On the

other hand, if we compare the results of treatment of patients with hay fever only with those in patients with hay fever and a complicating asthma, then the results are certainly poorer in the latter group: however, not because of their intranasal abnormality but, we believe, because we failed to find and remove other etiologic factors, probably of an allergic nature.

These observations, in our opinion, appear to show that hypersensitiveness to pollens and to substances other than pollens is the chief cause for a complicating asthma in hay fever patients and that nasal abnormality plays a minor rôle in this regard. It seems not unlikely that sinus disease and nasal polyps are in most instances secondary effects, not primary causes. On the other hand, we do not wish to minimize the importance of these nasal abnormalities. Of chief moment from the standpoint of allergy is the fact that these nasal abnormalities may in time introduce a bacterial factor as an additional etiologic agent of asthma. Furthermore, they serve to perpetuate respiratory infection which in turn will lead to bronchiectasis and emphysema; irreversible conditions which, once established, preclude the possibility of cure. It follows, then, that the adequate treatment of the nasal abnormality should be a part of the treatment of hay fever and its complications.

We admit that in an occasional case an intranasal abnormality, such as sinus disease, polyps or septum-turbinate pressure, must be corrected before specific therapeutic measures will be effective, although no such instance occurred in the group of treated cases here reported. We even admit that in a rare instance it has occurred that nasal surgery without specific treatment has cured a patient's hay fever. But we flatly challenge any statement[2] that nasal treatment alone, surgical or otherwise, routinely applied to all hay fever patients will give uniformly good results. We are accumulating evidence which will show that such nasal treatment alone will fail in all except the rarest instances.

A final point which may prove of interest is this: it was our impression that the usual course of events in the development by hay fever patients of a complicating asthma was that they first suffered

TABLE IX

TIME OF ONSET OF COMPLICATING ASTHMA IN HAY FEVER

(A)	HAY FEVER AND SEASONAL ASTHMA	27 cases
	Asthma began in first year	14 cases
	Asthma began in second year	3 cases
(B)	HAY FEVER, SEASONAL AND PERENNIAL ASTHMA	16 cases
	Seasonal asthma began in first year	10 cases
	Seasonal and perennial asthma began first year	7 cases
	Seasonal and perennial asthma began in same year	12 cases

from hay fever for a number of years, then began to have seasonal asthma for a few years, and finally developed perennial asthmatic symptoms.

We were surprised to find that in the majority of instances the asthma and hay fever began in the same season. In nearly one-half of the patients with both seasonal and perennial asthma, both types of asthma began in the first season of the hay fever. Furthermore, in 12 of the 16 perennial asthmatic patients, both the seasonal and the perennial forms of asthma began in the same season, although not necessarily in the first hay fever season. This may be due partly to the fact that our patients are practically all clinic cases and represent a level of society in which only those more severely affected, that is, with asthma as well as hay fever, would be likely to seek relief. However, a superficial examination of the records of private hay fever patients shows the same trend.

SUMMARY AND CONCLUSIONS

Clinical and roentgen-ray examinations of patients with uncomplicated hay fever and patients with hay fever and seasonal asthma show an incidence of sinus abnormality that is less than that in the average population.

When there is, in addition, a perennial asthma, there is a somewhat higher incidence of sinus disease.

Skin test findings and the results of specific treatment support the view that a complicating asthma is in most instances due to hypersensitiveness to pollens and to inhaled substances other than pollens, and not to the sinus disease.

Sinus disease is probably in most instances a secondary complication, not a primary cause of the asthma.

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(For discussion, see page 205.)

MAXIMUM DOSAGE IN POLLEN THERAPY*

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EXTRACTS

WHEN I first started to treat hay fever in 1920, and for several years thereafter, I used alcoholic-saline pollen extracts as advocated by Walker.[1] After innumerable comparative tests, however, I became converted to glycerine pollen extracts, and for the past six years have been using them exclusively. The chief point of superiority of the glycerine extracts is their stability. I learned by experience that aqueous or alcoholic-saline pollen extracts rapidly lose their strength, even when kept properly refrigerated, whereas glycerine extracts seem to retain their full potency for at least two or three years from the date of extraction. Glycerine pollen extracts that I prepared several years ago, are apparently just as potent today as freshly prepared extracts. Clock[2] was the first to advise the use of glycerine pollen extracts, his extracting fluid consisting of two-thirds glycerine and one-third saturated salt solution. By substituting a buffered salt solution (Coca's fluid) for the saturated salt solution, as suggested by Dr. Harry S. Bernton, and recommended by Armstrong and Harrison,[3] the fluid becomes definitely less irritating to the tissues; in fact, the individual doses of such an extract (67 per cent glycerine and 33 per cent buffered salt solution) may be injected without further diluting them with distilled water or normal saline solution at the time of injection. The buffered salt solution may be made by adding 2.7 grams of sodium bicarbonate and 5 grams of sodium chloride to 1,000 c.c. of distilled water. Because of the sodium bicarbonate, this solution will not stand boiling and must be sterilized by Berkefeld filtration. For the last two years, I have been using an extracting fluid consisting of 50 per cent glycerine and 50 per cent buffered salt solution. This extracting fluid maintains the potency and sterility of the pollen extracts just as satisfactorily as the Bernton, Armstrong and Harrison fluid, is even less irritating to the tissues, and is much easier to draw through small hypodermic needles.

It is desirable to prepare the extracts as concentrated as possible, in order that the very strong doses necessary for consistently perfect results, may be administered without injecting too large quantities of fluid. The question arises, therefore, as to what is the maximum concentration for glycerine pollen extracts. In the early part of 1927 I thought that 3 per cent pollen extracts were about as strong as could

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be prepared, with the use of the Berton, Armstrong and Harrison extracting fluid. Later in that same year, however, in cooperation with Swan-Myers Laboratory, I carefully performed comparative skin tests on a series of ragweed sensitive patients with 3, 4, and 5 per cent mixed ragweed (equal parts of short and giant) pollen extracts. An analysis of the reactions from these tests, showed the 5 per cent extract to be the most potent, the 4 per cent extract next, and the 3 per cent the least. There was very little difference, however, between the 3 and the 4 per cent extracts. A large number of nitrogen determinations on these same pollen extracts, showed that there was a regular increase of the nitrogen in the extracts, which increase was directly proportionate to the amount of pollen extracted.

In 1928, in cooperation with the same laboratory, comparative skin tests were made on a considerable number of ragweed sensitive patients, with 5, 10, 12.5, and 17.5 per cent mixed ragweed pollen extracts. A painstaking analysis of these tests showed the 12.5 and 17.5 per cent extracts to be tied for first place as the strongest reactor. The 10 per cent extract was second, and the 5 per cent extract was the weakest reactor. In other words, the 10 per cent extract was stronger than the 5 per cent; the 12.5 per cent and 17.5 per cent extracts were equal in strength, and stronger than the 10 per cent extract. From this it would seem that around 12 per cent is about as concentrated as mixed ragweed pollen extracts can be made, with this same extracting fluid of 67 per cent glycerine and 33 per cent buffered salt solution. Accurate nitrogen determinations showed a gradual and regular increase in the amount of nitrogen in the pollen extracts as the percentage of dry pollen extracted was increased. This increase occurred in a regular proportion up until the 12.5 per cent extract was reached. At this point the curve flattened out considerably, and while the 17.5 per cent and a 20 per cent extract were stronger in nitrogen than the 12.5 per cent extract, yet they were not proportionately stronger; and there was practically no difference between the 17.5 per cent extract and the 20 per cent extract. To put it in a simpler form, a 2 per cent extract was practically twice as strong as a 1 per cent extract. The 5 per cent extract was five times as strong as the 1 per cent. The 12.5 per cent extract was approximately twelve and one-half times as strong as the 1 per cent, but from there on up, the increase in nitrogen was very much less than the percentage of pollen would indicate. It may be seen, therefore, that the nitrogen determinations paralleled my clinical tests quite closely.

Starting in 1920 with 1 per cent pollen extracts, I have from year to year gradually increased their concentration, until I am now using 6 per cent and 10 per cent extracts. By a 6 per cent pollen extract is meant 6 grams of dry pollen to 100 c.c. of extracting fluid, and by a 10 per cent extract is meant 10 grams of pollen to 100 c.c. of fluid.

Noon[4] designated the equivalent of one-millionth of a gram of timothy pollen as one pollen unit. It has since been applied, however, to all types of pollen. In other words, 1 c.c. of a 10 per cent pollen extract would contain 100,000 pollen units or 100 milligrams of pollen.

In preparing the extracts, it is advisable to add some solid glass beads, not with the idea of macerating the pollen grains (which is unnecessary), but to facilitate shaking and prevent clumping, and thus allow the extracting fluid to come into contact with all of the pollen. The extracts are allowed to stand in the refrigerator for about one week with frequent, vigorous shaking; then they are Berkefeld filtered, and examined for sterility. Weaker dilutions are then prepared from this concentrated extract by diluting it 10, 100, and 1,000 times. These dilutions are prepared by taking nine parts of extracting fluid and one part of pollen extract to make the next weaker dilution. The use of the glycerine extracting fluid for preparing the various dilutions is quite important, as it maintains the potency and sterility of the dilutions for a year or two, and thus obviates the necessity of preparing fresh dilutions at frequent intervals. Some workers with glycerine pollen extracts make the mistake of using buffered salt solution in preparing the dilutions. Dilutions prepared in the latter manner contain so little glycerine that they are relatively unstable, which greatly increases the likelihood of constitutional reactions when changing to the concentrated extract for the final doses.

For the sake of convenience, I designate the three dilutions and the concentrated extract as *A*, *B*, *C*, and *D* strength respectively, which for the 6 and 10 per cent extracts would be as follows:

6 per cent

A = 60 pollen units or 0.06 mg. of pollen per c.c.
B = 600 pollen units or 0.6 mg. of pollen per c.c.
C = 6,000 pollen units or 6.0 mg. of pollen per c.c.
D = 60,000 pollen units or 60.0 mg. of pollen per c.c.

10 per cent

A = 100 pollen units or 0.1 mg. of pollen per c.c.
B = 1,000 pollen units or 1.0 mg. of pollen per c.c.
C = 10,000 pollen units or 10.0 mg. of pollen per c.c.
D = 100,000 pollen units or 100.0 mg. of pollen per c.c.

At the present time, I am using three different kinds of grass pollen extracts, namely, a timothy pollen extract, and two mixed extracts, one containing equal parts of four different grasses (June, orchard, perennial rye, and timothy), and the other, equal parts of six grasses (sweet vernal, June, orchard, perennial rye, timothy, and red top). Which extract to use in treating the individual grass-sensitive patient is determined by the skin reactions. Where the dominant reaction is to timothy

dry pollen or to one of the timothy pollen fractions, that grass extract which gives the largest reaction of the three is selected for treatment. Where the dominant reaction is to one of the grasses other than timothy, the mixed grass extract which gives the larger reaction of the two is chosen for treatment.

Similarly, I am using two different kinds of ragweed pollen extracts, namely, a short ragweed pollen extract, and a mixed extract containing equal parts of giant and short ragweed. Where the dominant skin reaction is to short ragweed dry pollen or to one of the short ragweed pollen fractions, the ragweed extract which gives the larger reaction of the two is selected for treatment. Where the dominant reaction is to giant ragweed or to one of the fractions of this pollen, the mixed ragweed extract is used for treatment.

TREATMENT

Seasonal hay fever patients are advised to start treatment about six months in advance of their season. The treatment consists of a series of gradually increasing doses of the specific pollen extract, injected subcutaneously by means of a sterile hypodermic syringe and a small sharp needle. The doses are given in the outer part of the upper arm about midway between shoulder and elbow, at a site corresponding to the insertion of the deltoid muscle. As a rule, first one arm and then the other is utilized for the treatments.

The treatments are administered from a day to a week apart, depending upon the amount of time available before season, and the duration of the local reaction. When there is plenty of time for desensitization, the weekly interval seems to be ideal, but if the time is short, the treatments are given closer together. A good way to estimate the proper interval between doses is as follows: If a patient starts treatment five months before season, the injections are given every six days; if he starts four months before season, the injections are made every five days; if three months before season, injections every four days; two months before season, every three days; one month before, every other day. A safe general rule is not to give another treatment until the local reaction from the preceding dose has disappeared. Under pressure, *A* strength doses may usually be given every day; *B* strength doses, every other day; *C* strength, every third day; and *D*, every fourth day.

The individual doses of extract must be measured with extreme accuracy, a tight tuberculin syringe being necessary for the purpose. The initial dose of pollen extract is usually from 3 to 10 units (0.05 to 0.1 c.c. of *A* strength), depending upon the degree of skin sensitivity. Each subsequent dose is regulated principally by the amount of local reaction from the preceding one. With the average patient, the dose can be doubled each time on the weaker dilutions (*A* and *B* strengths). Every patient is instructed to inspect his arm carefully at bedtime of

the treatment day, and again the next day about twenty-four hours after the injection, to see whether there is a pink spot about the site of injection, and if so, about how large it is each time; also to note whether there is any itching, swelling, fever, hardness, or soreness of the arm both times. As a rough guide, it may be said that if any dose of *A* or *B* strength fails to give a satisfactory local reaction, the next dose is more than doubled. If a local reaction is present at bedtime but gone entirely in twenty-four hours, the next dose is increased two and one-half times; if no local reaction at either time, the next succeeding dose is tripled.

On *C* strength, the dose is usually increased each time by 0.05 c.c., or a multiple thereof, depending upon the reaction from the preceding dose. Special care is used when changing from *C* to *D* strengths, and in fact with all injections of the concentrated extract, where every 0.01 c.c. of 6 per cent extract is equivalent to 600 pollen units, and each 0.01 c.c. of 10 per cent extract equivalent to 1,000 units. In administering *D* strength, the dose is never doubled, but is increased each time by 0.01 c.c., or a multiple thereof, depending upon the reaction from the preceding treatment. For example, if an increase in dosage of 0.01 c.c. of *D* strength fails to give a satisfactory local reaction, the next dose is increased by 0.02 c.c., and so on; but if any particular increase in dosage gives a perfectly satisfactory reaction, then the next succeeding dose is increased by the same amount. In judging how much to increase the doses, it is very helpful to inquire as to whether the local reaction from the previous treatment is more, the same, or less than the reaction from the treatment just preceding that one. If any dose produces a severe local reaction (erythema or swelling extending below the elbow), the same sized dose is repeated for the next treatment, and then increased less rapidly following that.

If, for one reason or another, a patient's treatments are interrupted, it becomes necessary to decide what dose to give when treatment is resumed. If approximately two weeks have elapsed since the last treatment, I repeat the same dose instead of increasing it. If approximately three weeks have elapsed, I go back to the dose of the next to the last treatment, and so on. In other words, I take the number of weeks that have elapsed since the last treatment and subtract one, which gives me the number of treatments to count back to arrive at the proper dose.

If an immediate constitutional reaction in the form of hives or an attack of hay fever or asthma follows any treatment, a tourniquet is quickly applied to the arm above the site of injection, and 0.5 c.c. to 1 c.c. of epinephrine chloride solution (1 to 1,000) is injected subcutaneously in the opposite arm, at once, and repeated if necessary. The sooner a constitutional reaction manifests itself following an inoculation, the more severe it is likely to be. Fortunately, however, with sufficient care in regulating the doses, and proper technic in admin-

istering them, constitutional reactions rarely occur. The most severe constitutional reactions are due to accidentally entering a small vein with the needle, the extract thus being injected directly into the blood stream. When this occurs, the patient develops constitutional symptoms almost instantaneously. As a precaution against this, after the needle is inserted in the arm and before the extract is injected, the piston of the syringe is withdrawn sufficiently to see an air space between the extract and the needle-end of the syringe; if a trace of blood shows in this space, the needle is withdrawn and inserted in another spot. The extract is injected slowly, and the piston of the syringe is withdrawn several times during the injection, to make sure that the needle has not entered a blood vessel. After the extract is injected, a small pledget of cotton, moistened with alcohol, is pressed over the site of injection, and held there while the needle is being withdrawn and for a short time thereafter, to prevent any of the extract from tracking back through the needle wound into a superficial vessel that may have been punctured by the passage of the needle through the tissues. I consider this last precaution quite important in the prevention of constitutional reactions.

Following the stronger doses, the patients are kept in the office for a while, about fifteen minutes for *C* strength, and about one-half hour for *D* strength. The advantage of having the patients wait is that if constitutional symptoms begin to develop, such as itching of the palms of the hands, or irritation of the throat or nose, epinephrine may be administered without delay, thus checking the reaction or greatly reducing its severity. Furthermore, constitutional reactions are not so likely to occur if the patients remain quiet for a while, because exercise, especially in hot weather, increases the circulation, and therefore causes the pollen extract to be absorbed more rapidly. Glycerine extracts are absorbed slower than aqueous extracts, and consequently are less likely to produce constitutional reactions.

The maximum dose of pollen extract that I seek to attain is from 60,000 to 100,000 pollen units (1 c.c. of 6 or 10 per cent extract). Whatever maximum dose is reached just before the pollen season, is repeated at weekly intervals throughout the season. If any individual coseasonal dose is followed within twenty-four hours by a definite aggravation of hay fever symptoms, the next dose is reduced a little. At the termination of the pollen season, I start increasing the doses again, and continue the treatments throughout the year until the patient seems to be as completely desensitized as possible. When the maximum dose of 60,000 to 100,000 pollen units is reached, this dose is repeated at weekly intervals until it fails to give a twenty-four hour local reaction, and then the interval between the treatments is gradually widened. When the positive skin reactions disappear, that is, when scratch tests with whole

dry pollen and with *D* strength extracts are completely negative, the treatments are stopped entirely.

CASE REPORTS

It seems unnecessary to tabulate my results with this method of treatment, as they have been almost monotonously perfect. However, I shall report briefly some typical cases to illustrate certain phases of the subject.

CASE 1.—Mr. D., aged thirty-eight years, was referred to me with fall hay fever and asthma of ten years' duration. Each year his trouble started the latter part of August and continued until frost. His eyes itched a lot during this season of the year, and at no other time. Cutaneous tests were completely negative, but ophthalmic tests with whole dry pollen of giant and short ragweed were definitely positive. Starting in March, 1928, he was treated at weekly intervals with rapidly increasing doses of mixed ragweed pollen extracts, reaching 50,000 pollen units in July, 1928, and 60,000 units in January, 1929. This maximum dose of 60,000 pollen units was repeated at widening intervals until October, 1929, when the treatments were stopped. No constitutional reactions occurred at any time. As a result of this treatment, he has had no further symptoms of autumnal hay fever or asthma.

CASE 2.—Miss B., a pale, sickly looking child of 11 years, was brought to me suffering with asthma of five years' duration, which I found to be due to sensitization to ragweed pollen. She was treated with mixed ragweed pollen extracts, starting in March, 1928, with 5 pollen units, and the doses were gradually increased at weekly intervals, until a maximum of 60,000 units was reached in May, 1929. This maximum dose of 60,000 pollen units was then repeated at widening intervals until October, 1929, when the treatments were stopped. No constitutional reactions occurred. She gained about 20 pounds in weight during this course of treatment, and seems to be entirely well of asthma.

CASE 3.—Mr. R., aged thirty-six years, was referred to me in July, 1927, with typical fall hay fever, which he had suffered with during four consecutive seasons. Skin tests showed this trouble to be due to marked sensitization to short and giant ragweed pollen. Treatment was started on July 19, 1927, with 4 pollen units of mixed ragweed extract, and by August 22, 1927, this had been increased to 1,680 units, which maximum dose was repeated at weekly intervals until September 20, when the treatments were discontinued. As a result, his hay fever was definitely better that season. Treatment was resumed on March 14, 1928, with a dose of 5 pollen units of mixed ragweed extract, which by August 21, 1928, had been increased to 25,000 units. As a result of the relatively strong doses, he had practically no hay fever that fall, and treatment was discontinued on September 18, 1928. His treatments were started again on May 13, 1929, with a dose of 6 pollen units, and since then he has been treated perennially. By the middle of August, 1930, he was getting 49,200 pollen units, and went through the entire season without the slightest symptom of hay fever. His most recent dose was 150,000 units or 1.5 c.c. of 10 per cent extract. He has never had a constitutional reaction. Ragweed retests on this patient have shown a progressive and marked reduction in skin sensitivity, and I am continuing to increase his doses with the hope of making the skin reactions disappear.

CASE 4.—Mr. M., aged thirty-one years, was referred to me in August, 1927, with clear-cut seasonal hay fever, which he had suffered with every fall since he was sixteen years old. He had been given preseasonal ragweed treatments by

another physician four different years. Although these treatments helped some, they had never prevented him from having hay fever. Skin tests confirmed his sensitization to ragweed. His reactions were very large, scratch tests with whole dry pollen of giant and short ragweed producing urticarial wheals over two inches in diameter. I gave him specific coseasonal treatment in the fall of 1927, with very good results. Preseasonal treatment was started in March, 1928, with 5 pollen units of mixed ragweed extract, and the doses were gradually increased. By August 13, 1928, he was getting 13,500 units, which dose was repeated once a week until October 9, 1928, when I started increasing his doses again. He had very little hay fever during the fall of 1928. His treatments were continued perennially at weekly intervals until a dose of 60,000 pollen units was reached on June 4, 1929. This dose of 60,000 units was repeated at widening intervals until October 5, 1929, when treatment was discontinued. During the fall of 1929 he had absolutely no hay fever. He was retested in June, 1930, and as he still showed some skin reaction to ragweed pollen, treatment was resumed and has been continued perennially since then. He went through the fall of 1930 without the slightest symptom of hay fever, in spite of driving around the country during the season in an open automobile. His most recent dose was 96,000 units, and he has never had a constitutional reaction.

CASE 5.—Mrs. R., aged forty-eight years, was referred to me in August, 1927, with uncomplicated fall hay fever of about six years' duration. She had been given preseasonal (April to August) ragweed inoculations by another physician, with very little benefit. Her only real relief had been obtained by going to northern Canada during the season. Skin tests showed her to be definitely sensitive to short and giant ragweed pollen, and specific coseasonal treatment during the fall of 1927 gave her considerable relief. Preseasonal treatment was instituted in March, 1928, with a dose of 2.5 pollen units of mixed ragweed extract, and she entered the 1928 hay fever season with a dose of 11,000 units. She had very little hay fever that season, and treatment was discontinued on September 19. Her treatment was started again in April, 1929, with a dose of 3 pollen units of mixed ragweed extract, but by the season she had built up to only 9,600 units. As a consequence, she had more hay fever in 1929 than she had had the previous year. Her 1930 preseasonal treatment was started in March, and when the season arrived she was getting 52,200 pollen units, which dosage gave her a practically perfect season. This patient's 1931 treatments were started in April with a dose of 5 pollen units of short ragweed extract, and her most recent dose was 67,000 units. She has had only two constitutional reactions, which were mild and followed doses of 3,000 and 10,500 units respectively, administered in 1928.

CASE 6.—Mr. E., aged fifty-three years, was referred to me in February, 1928, with a history of spring hay fever. Skin tests were all negative, with the exception of definite positive reactions to the pollen of various species of oak trees. Treatment with a mixed oak extract was started on March 1, 1928. By April 13, 1928, he was getting 7,800 pollen units, which dose was repeated at weekly intervals until May 9. As a result he had a very comfortable season, although he was not entirely free of hay fever. His treatment was resumed on December 7, 1928, and by April 1, 1929, he was getting 60,000 pollen units. This maximum dose was repeated until August 10, 1929, when treatment was discontinued. He had absolutely no sign of hay fever during the spring of 1929, and since then has had no further treatment and no hay fever. He never had a constitutional reaction from treatment.

CASE 7.—Mr. N., aged forty-five years, was referred to me in February, 1928, with a history of having seasonal hay fever as far back as he could remember. He had hay fever from May until frost, and during the preceding season had developed

asthma. A large number of tests by another physician had shown him to be sensitive to timothy and ragweed pollens, but treatment on this basis had given him very little relief. When I tested him, I found him to be moderately sensitive to grass and mildly sensitive to ragweed, but his dominant reaction was to the pollen of English plantain. I started his treatment on March 2, 1928, with 5 pollen units of plantain extract, and by May 8, 1928, the dose had been increased to 21,500 units. As a result, he had hardly any hay fever that season, and treatment was discontinued on September 25, 1928. He resumed treatment on March 20, 1929, with 6 units of plantain extract. By May 14, 1929, he was getting only 6,000 pollen units, and with this smaller dosage did not have so good a season as the preceding year. His treatment was continued perennially until February 9, 1930, at which time he was getting 60,000 units of plantain extract. All of the treatments were administered at his home under my direction, and there were no constitutional reactions. Although he took his last treatment in February, 1930, he had absolutely no sign of hay fever during the 1930 season, and has had no trouble this year. As is usually the case, when sufficiently intensive treatment is given against the primary reactor (in this instance, plantain), the secondary reactors (grass and ragweed) can be ignored.

CASE 8.—Mrs. A., aged forty-two years, was referred to me in May, 1928, for the treatment of seasonal hay fever, which she had had every fall for eighteen years, except when in Europe. She had been treated for several years by others with ragweed pollen, and although their inoculations had helped her, they had never kept her free of hay fever. I started to treat her on May 4, 1928, with 2.5 pollen units of short ragweed extract, and by August 29, 1928, had increased her dose to 44,500 units. Treatment was discontinued on September 28, 1928, and she estimated her result that season as 98 per cent improved. I retested her in February, 1929, and her skin reactions to short and giant ragweed showed a marked reduction in comparison with what they had been when she first came to me. Treatment was resumed on March 5, 1929, with 3 pollen units of mixed ragweed extract, and by August 14, 1929, had been increased to 51,600 units. As a result, she went through the fall of 1929 without the slightest symptom of hay fever. A good many of the larger doses were given by her own family physician in Rhode Island, under my direction. She never had a constitutional reaction, in spite of her insisting that all of the doses be injected as rapidly as possible. Treatment was continued perennially until January 3, 1930, and although she has taken no treatment since, had an absolutely perfect season in 1930. When I retested her in November, 1929, she gave no reaction to giant ragweed whole dry pollen, and only slight or doubtful reactions to short ragweed whole dry pollen and *D* strength extracts. Tests in April, 1930, with various fractions of giant and short ragweed pollen gave very slight or doubtful reactions, showing a high degree of desensitization.

CASE 9.—Mrs. H., aged thirty-two years, was referred to me in May, 1928, for the treatment of fall hay fever of about twenty-five years' duration. She had hay fever from August 21 until frost, and had never missed a season since the trouble started. She had taken ragweed inoculations at different times from other physicians, but they did not help her. She reacted to giant and short ragweed pollen, and my treatment was started on June 28, 1928, with a dose of 2.5 units of mixed ragweed extract, which by August 15, 1928, had been increased to 1,850 units. She had a fairly good season that year, and treatment was discontinued on September 21, 1928. Her treatment was resumed on March 1, 1929, with 3 units of mixed ragweed extract, and by August 15, 1929, she was getting 8,400 units. She had very little hay fever during the fall of 1929, and treatment was stopped on October 3, 1929. Treatment was started again on March 11, 1930, with 6 units of mixed ragweed extract, and has been continued perennially since then, her most

recent dose being 83,000 units. She entered the 1930 season with a dose of 20,400 units, and had a perfect season with the exception of slight nasal irritation on the afternoon of September 4. This patient has had two mild constitutional reactions following doses of 54,600 and 62,000 units respectively, both of which were due to some of the extract accidentally getting into the blood stream.

CASE 10.—Mr. C., aged thirty-five years, was referred to me in May, 1928, with fall hay fever of twelve years' duration. He had had this trouble every August and September, with the exception of 1917 and 1918 when he was in Europe. He had taken treatment since 1920, but the inoculations had given him only slight relief. Skin tests showed him to be moderately sensitive to short and giant ragweed pollen, and I started treating him on May 24, 1928, with a dose of 5 pollen units of mixed ragweed extract, and have been treating him perennially ever since. By August 13, 1928, his dose had been increased to 6,500 units, and although he had a decidedly better season that year, he still had hay fever. By the fall of 1929, he was getting 40,200 units, which dosage gave him a perfect season. When the fall of 1930 arrived, he had reached a dose of 60,000 units, and had another absolutely perfect season. His most recent dose was 90,000 units, and he has never had a constitutional reaction. Occasional retests have shown a progressive reduction in skin reactivity to ragweed pollen, and the last tests in March, 1931, with concentrated 6 and 10 per cent extracts were negative. As evidence that this patient is attaining practically complete desensitization, my office nurse, while giving him a 60,000 unit dose, accidentally got into a vein and injected the entire amount before she discovered it. The patient almost immediately experienced a slight feeling of dizziness and a mild irritation of the throat, but other than these very transitory symptoms, had no ill effects from what was probably the strongest dose of pollen extract ever administered intravenously to a hypersensitive person. It was not necessary to resort to epinephrine or ephedrine. As proof that the entire dose was injected into the blood stream, there was absolutely no sign of a local reaction on the right arm, either immediately or later, whereas when a dose of this size is injected subcutaneously it is always followed by a good-sized lump on the arm. Furthermore, there was a cluster of hives about the sites of former injections in the left arm.

CASE 11.—Master H., thirteen years of age, was brought to me in August, 1928, with asthma, from which he had suffered since he was a tiny baby. I found his asthma to be due to sensitization to short ragweed pollen, and started specific treatment on November 16, 1928, with 6 pollen units of short ragweed extract. This treatment has been continued perennially since then, and by June 21, 1930, the dose had been increased to 60,000 units. Ragweed retests in November, 1930, were completely negative. He has never had a constitutional reaction, and under this form of treatment has gotten entirely well of his asthma, and gained about 60 pounds in weight.

CASE 12.—Mr. W., aged forty-two years, was referred to me in August, 1929, with typical fall hay fever of about ten years' duration. Skin tests showed this trouble to be due to marked sensitization to ragweed pollen. Treatment was started on August 21, 1929, with a dose of 3 pollen units of mixed ragweed extract, and has been continued perennially since then. His hay fever was greatly relieved by the coseasonal doses during the fall of 1929. By April, 1930, he was getting 60,000 units at a dose, and as a result had an absolutely perfect 1930 season. Ragweed retests on this patient have shown a marked reduction in skin sensitivity. His most recent dose was 96,000 pollen units, and he has never had a constitutional reaction, and practically all of the treatments have been administered by his family physician, under my direction.

CASE 13.—Master B., fifteen years of age, was referred to me in November, 1929, with asthma. This was found to be due to sensitization to short ragweed pollen, and specific treatment was started on January 27, 1930, with a dose of 6 pollen units. The treatments were continued perennially at weekly intervals until February 25, 1931. He reached a maximum dose of 60,000 pollen units on January 14, 1931, and there were no constitutional reactions. Ragweed retests in February, 1931, with whole dry pollen and concentrated 6 and 10 per cent extracts, were completely negative, whereupon the treatments were stopped. Since the institution of this form of treatment, Master B. has been entirely well of asthma, and has gained over 10 pounds in weight.

CASE 14.—Mrs. E., aged fifty years, was referred to me in January, 1930, for the treatment of unusually severe ragweed hay fever, with which she had suffered every fall for at least seventeen years. Following local treatment by several competent rhinologists, she had been treated with inoculations of ragweed pollen extracts for eleven consecutive years. In the beginning, these inoculations had given her about 25 per cent relief, but in recent years, her hay fever had gotten progressively worse in spite of the treatments. I started to treat her on January 31, 1930, with a dose of 6 pollen units of mixed ragweed extract, and have continued her treatments perennially since then. By August 14, 1930, she was getting 31,200 units, and as a result of this dosage, went through the entire season without any symptoms of hay fever. This patient's last dose was 60,000 pollen units, and she has never had a constitutional reaction; practically all of the doses have been injected by other physicians.

CASE 15.—Mr. F., sixty-three years old, was referred to me in March, 1930, with late spring or summer hay fever, which he had had every year without fail since he was twenty-two or twenty-three years of age. His hay fever started each year between May 15 and June 1, and lasted until the latter part of July. Skin tests showed a very marked positive reaction to English plantain pollen, and moderate positive reactions to grass pollens. The next day following the tests, there was still a large, red, itchy spot at the site of the plantain test, whereas the grass reactions had completely disappeared. I started his treatment on March 25, 1930, with 3 pollen units of English plantain extract. By May 13, 1930, he was getting 1,440 units, which dose was repeated at weekly intervals until July 15, 1930, when I started increasing his doses again. He had very little hay fever during the 1930 season. He stopped treatment the first of June, 1931, with a final dose of 52,000 units. There were no constitutional reactions from treatment, and practically all of the doses were injected by his home physician. He has already passed the peak of the 1931 plantain season without the slightest sign of hay fever.

CASE 16.—Mr. T., aged twenty-four years, was referred to me in June, 1930, with late spring or summer hay fever, which he had had for about four years. Skin testing showed this trouble to be due to sensitization to the pollen of the common grasses. His treatment was started on June 9, 1930, with 6 pollen units of mixed grass extract, and he was given small coseasonal doses until July 27, 1930, when the treatments were temporarily discontinued. As a result of this treatment, he had a very comfortable season. The mixed grass treatments were resumed on September 5, 1930, with a dose of 9 pollen units, and have been continued at weekly intervals since then. By May 7, 1931, he was getting 45,600 units. Nearly half of his treatments have been administered by out of town physicians, under my direction, and there have been only two very mild constitutional reactions, following doses of 1,560 units and 36,000 units respectively. He has already passed the peak of the 1931 grass pollinating season, without the slightest symptom of hay fever.

COMMENT

In 1926, Rackemann, Graham and Scully,[5] from an intensive study of their results in 54 patients with late hay fever treated with ragweed pollen extract during four or more years, observed that in at least 14 per cent of the cases it was possible to show that excessive dosage was responsible for the poor end-results, and that in many instances the result was much better when a smaller dose and a less vigorous course of treatment was employed. From this they concluded that success in the treatment demands a course of doses of a size and extent which is "optimal" for the particular patient. Rackemann has again expressed this same opinion in his recent book.[6] A careful study of their charts convinced me that their error lay in continuing to increase the doses during season, which in combination with the pollen absorbed from the air was too much for the patients and consequently aggravated their hay fever.

SUMMARY AND CONCLUSIONS

Providing that extracts of the causative pollens are used, the results in the treatment of seasonal hay fever or pollen asthma are directly proportional to the size of the maximum dose attained before season.

By gradually working up to large enough preseasonal doses, namely, 60,000 to 100,000 pollen units, failures are eliminated from hay fever therapy, and perfect results practically assured. To administer such strong doses, it is necessary to give up to 1 c.c. of 6 to 10 per cent pollen extracts. Although these doses are much larger than are being used by other workers in the field of allergy, my extensive use of them indicates that they may be given with perfect safety and comfort, providing sufficient care and judgment are used in regulating the preliminary increases in dosage in the individual patient.

Furthermore, the evidence at hand would seem to indicate that the administration of such massive doses leads to complete and permanent desensitization, with a disappearance of positive skin reactions.

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(For discussion, see page 199.)

URTICARIA SOLARIS

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THE purpose of this report is to present an unusual case of physical allergy occurring in a light-sensitive patient, characterized by general as well as local manifestations, to review similar cases previously reported, and to discuss some interesting features of the etiology and pathogenesis of this disorder.

CASE REPORT.—A. L. K., a white man, aged thirty-two years, consulted me first in September, 1924. He complained of swelling and itching of the face and neck, of seven years' duration, much worse in the last six months. He volunteered the information that the condition was always worse in summer and that it was limited almost entirely to the face and neck. He did not know what produced an attack, which occurred with great rapidity, was accompanied by a little swelling of his hands, and a state of mental obtundity and psychical depression.

The family history was negative for allergic disease. As a child he suffered from hives. He stated that he had malaria ten years before; otherwise the past medical history was negative.

The patient was a robust, well-nourished man whose general physical examination was negative except for questionable tonsillar infection and a low blood pressure which averaged about 90 mm. systolic and 60 m.m. diastolic.

Laboratory studies seemed unimportant. The blood count, the blood Wassermann and blood chemistry tests were all normal. Urine analysis was reported as a slightly increased number of white blood cells in the sediment on several occasions. He was skin-tested for all of the common foods and inhalant substances with negative results. Then, because of the history of malaria, 30 grains of quinine were given as a provocative dose but failed to produce any reaction, and the blood remained negative for malarial organisms.

Working on the assumption that this might be a case of sensitiveness to light I had the patient's face and neck exposed to the quartz lamp at a distance of 24 inches for three minutes at about 3 o'clock in the afternoon. By 7:30 P.M. that evening there were swelling and itching of the face and a swollen V-shaped area of redness and itching on the anterior chest. Some relief from itching followed an injection of adrenalin. Redness and swelling were present the following day.† I then spoke to him concerning my belief that he had a peculiar sensitiveness to light and after this lead he told me that on one occasion after standing bareheaded in the sun for two hours he had developed an attack and on another occasion while driving with his sleeves rolled up and the windshield open, his arm became swollen where exposed and the covered portion was unaffected. He also informed me that unconsciously he chose the shady side of the street because he felt stuffed up and uncomfortable on the sunny side. While under my observation, following a long drive in an automobile during which time he was unable to keep wholly out of the

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†The normal reaction to an exposure of a mercury vapor lamp to the skin of the forearm for from three to six minutes at a distance of 18 inches is reddening of the skin which begins to appear in thirty to sixty minutes and deepens during the following hour. In the following day or day after, the skin is a little swollen and tender to greater or lesser degree (Thomas Lewis[1]).

sun, he had a severe attack. His hands were swollen so that he could not take a ring off of his finger. The penis also became swollen on this occasion and according to his statement, possibly the feet as well. Slowness of speech and manner were present. Partial relief followed the administration of adrenalin and calcium. The patient complained of "nervousness" for several weeks after this attack.

The patient last consulted me in November, 1924. Subsequently I heard from Dr. W. H. Bunn of Youngstown, whom he had consulted, that he had had an attack of swelling and itching of the face and that adrenalin had failed to give relief. The patient previously had been advised to avoid direct exposure to the sun and had been put upon a constant dose of calcium and advised to have adrenalin injections for the immediate treatment of the attacks. The patient was then lost track of and efforts to trace him have been unsuccessful.

Our attention was first focused on urticaria as a manifestation of sensitiveness to light by Duke[2] who in 1923 published a case and certain observations which are here abstracted.

A married woman, aged forty-three years, a number of whose relatives were subject to seasonal hay fever, asthma and urticaria, had observed for four years that the skin itched intensely and broke out with wheals whenever she was exposed to sunlight; and whenever a sufficient area of skin was exposed, she became seriously ill. On one occasion, temporary blindness followed exposure of the face to sunlight.

Physical, laboratory and roentgen ray examinations, and intracutaneous tests, revealed nothing of interest.

On testing, it was found that hives could be produced by exposure to any type of light that contained violet rays; namely, by the light of a nitrogen lamp, arc light, sunlight, or mercury vapor quartz light. The skin was unaffected by ordinary exposures to the roentgen ray or to colored light except blue violet. Exposure of the skin for thirty seconds to summer sunlight was followed within a few minutes by erythema and itching, and within five minutes or less by the appearance of a typical hive which would cover the entire area exposed, but which never extended with pseudopod formation beyond the area exposed.

Exposure of a considerable area of skin was followed by an eosinophilia (8 per cent). The subcutaneous injection of epinephrin (1 c.c.) did not prevent the reaction on exposure to light. A reaction was followed by temporary exhaustion of the skin locally, so that further applications of light on the same day produced less or no reaction.

Application of light at daily intervals was associated with a considerable degree of local tolerance, so that, after repeated applications of light, a twenty-five-minute exposure produced less effect on the skin than could be produced by a two-minute exposure of untreated areas. No marked increase in tolerance of the skin generally followed this treatment. (The word "tolerance" is used here in a very general way, for the apparent local tolerance may have been partly the result of an exhaustion process.) After a time this tolerance was lost, and telangiectases appeared over the treated areas. In harmony with this, it may be mentioned that the face, neck, hands and forearms, which are, of course, naturally exposed to light at frequent intervals, were much more tolerant of light than covered areas, such as the chest, shoulders and back.

Every effort to produce hives by such agents as heat, rubbing, scratching, by the application of chloroform liniment, and by intracutaneous injections produced no visible effect unless the skin was simultaneously exposed to light.

Duke called attention to two previous case reports. One by Ward[3] in 1905 entitled "Erythema and Urticaria, with a Condition Resembling Angioneurotic Edema Caused Only by Exposure to the Sun's Rays" occurred in a woman of forty-seven years who had a typical urticarial reaction following exposure to the sun, which Ward proved by the use of colored glass was due to the actinic ray. He observed that the patient reminded him of cases in which the skin remained sensitive to changes of temperature after once having been frozen. Duke also mentioned a case reported by Ochs[4] in 1910, of a woman aged thirty-four years, who developed urticaria from exposure to the sun's rays. Since Duke's report cases have been added to the literature by Beinhauer,[5] Frei,[6] Pasteur Vallery-Radot, et al. (one in 1926[7] and another in 1928[8]), Wucherpfennig[9] and Sellei.[10]

In a paper devoted to urticaria caused specifically by the action of physical agents, Duke[11] speaks of urticaria solaris as a contact reaction which he says is a distinct type of reaction characterized throughout by the following phenomena:

1. The patients gave a family history of hay fever, asthma or hives.

2. A local reaction, characterized by erythema, itching and edema, was brought out specifically by the action of one or two physical agents, and could not be produced by other agents, including the intracutaneous injection of a large variety (more than 300) of substances.

3. The reaction failed to spread with pseudopod formation beyond the area directly exposed.

4. The skin was exhausted locally by reaction.

5. Local tolerance followed frequent exposures.

6. Symptoms of general (or constitutional) reaction, such as collapse and eosinophilia, followed the reaction of large areas of skin.

7. Reactions, although stopped locally by an injection of epinephrin, were not affected by the subcutaneous injection of ordinary amounts (from 0.5 c.c. to 1 c.c.) of epinephrin at distant points.

Duke then discusses various theoretical explanations of contact reactions as follows:

1. The patients, coming as they did from hay fever, asthma or hives families, may have actually become specifically hypersensitive to some product generated in their own tissues under the influence of a physical agent.

2. Through the influence of some abnormal condition, such as hematoporphyrinemia, or exposure to roentgen ray, radium ray, actinic ray or some other agent, some protein body may have been so altered that it could be split through the specific action of a physical agent, with the liberation of a histamine-like body.

3. Through the action of some substance, possibly such as hematoporphyrin and light, or roentgen ray or actinic ray, the temperature at which certain organic bodies could jellify or tend to coagulate might have been so changed that aggregation of their molecules could be caused by the action of physical agents, so that direct damage to certain tissue cells could be produced by them even in the amounts encountered under natural conditions.

It may be mentioned here that animals can be so sensitized to light by the intravenous injection of hematoporphyrin that a relatively short exposure to light results fatally; the *Paramesia caudatum* can be so sensitized to heat through the action of the actinic ray, radium ray or roentgen ray that a rise of temperature of a few degrees results fatally; that egg white can be coagulated at room temperature through the action of the actinic ray and by ordinary sunlight if hematoporphyrin is added to the solution; and, finally, that the temperature at which albumin coagulates and gelatin liquefies can be lowered through the action of physical agents, such as the roentgen or the actinic ray.

It seems not impossible, in view of these experiments, that an aggregation of protein molecules might occur intracellularly under the action of certain physical agents, and in this way give rise to an insult to the cell which could cause a reaction locally and, in case of involvement of large areas of skin, could set free poisonous bodies which could give rise to general reaction and collapse. In view of the negative results obtained by the intracutaneous injection of the serums of Duke's patients into normal individuals and hay fever patients followed by exposure of the injected areas to the action of the physical agents mentioned, one would be inclined to believe that the substances responsible for the reaction in these cases reside in the tissue cells rather than in the plasma.

4. According to the experiments of Janet Clark, the various proteins of plasma, if separated from plasma and purified, can be coagulated by the action of actinic ray. Plasma itself, however, cannot be coagulated in this way. According to her view, the plasma contains protective substances that hinder light rays from coagulating its protein. The existence of such substances would seem theoretically quite necessary for the protection of the surface protein, especially in animals that are exposed frequently to light. It seemed quite possible that the sensitiveness of the patient whose history is cited might be accounted for through a lack of such protecting bodies, and that similar mechanisms might be involved in patients sensitive to heat and cold.

The serum of the light-sensitive patient was studied from this point of view, however, both by Clark and by Duke, and found to behave like normal serum on exposure to light.

Beinhauer's case occurred in a man of twenty years with a family history of allergy. He obtained a positive reaction to the mercury lamp and proved that the nearer ultraviolet rays were responsible by using nickel-oxide glass as a filter. Adrenalin controlled and modified the reaction. The blood and urine were negative for hematoporphyrin. Duke had previously mentioned the case of Betz who had sensitized himself to light by the intravenous injection of 0.2 grams of hematoporphyrin. Exposure to sunlight caused edema and itching and this sensitiveness to light persisted for several months.

The cases reported by Pasteur Vallery-Radot and associates both occurred in women and corresponded to the picture already described. No new observations were recorded. The most important paper dealing with the subject since Duke's observations is that by Wucherpfennig who made a quantitative and qualitative study of light-sensitive patients using the light wheal as a biologic test. He described three cases in women using the term "urticaria photogenica." Tests were made on the three light-sensitive patients with the following sources of light: a high sun lamp (quartz light), Kromayer without filter, Kromayer with a blue glass filter, an electric arc with simple carbon, an ultraviolet lamp with nickel-oxide glass filter. Sollux (sunlight lamp) without filter and the same lamp with blue, green, orange and red filters. Maximum light hypersensitiveness was made out in the visible light spectra. In one patient all rays except the red ray could bring out the light wheal. The first patient's blood was tested for hematoporphyrin but none was found. The suggestion was made that it might be found only during an attack. The patient had eaten buckwheat cakes shortly before the attack and attention was called to a fluorescent sickness of sheep due to the eating of buckwheat.* It also was suggested that the chlorophyll of ingested foods might not be successfully metabolized and result in a hypersensitiveness to light. Patients were tested by placing them on a high spinach and green vegetable diet, collecting the blood serum on agar plates, adding washed human blood corpuscles, dividing the plates into sectors and exposing these sectors to light in increasing amounts to see if hemolysis occurred. The results were negative.

The author called attention to the possibility of an association of this disorder with alterations in genital function. In all three of his patients the condition seemed intimately associated with disturbances in the menses.

Normal, light-sensitive and urticaria factitia patients were tested as to their sensitivity to histamine. A similarity was noted between a light wheal and the histamine reaction in regard to both the mechanism of origin, and the form and position of the wheal. Wucherpfennig

*An interesting discussion of buckwheat poisoning (Fagopryismus) in animals occurs in an article by Smith[12] who reported a remarkable case of sensitiveness to buckwheat in man.

concluded that in these patients it was quite likely that in addition to the urticarial substances formed by exposure to light there was also an increased preparedness of the vessels of the skin for wheal formation.

Urticaria as an allergic reaction, and allergy as a state characterized by diminished resistance to histamine-like substances is a recent concept which has found support in the studies of Thomas Lewis and associates on the blood vessels of the skin and their responses. Lewis in a series of studies over a period of years developed the theory of the release by injury of a nonspecific histamine-like substance, generally referred to as H-substance, normally present in the skin cells, as responsible for a triple response, consisting of local dilatation of minute vessels, widespread arteriolar dilatation and whealing. This response could be brought about by mechanical, electrical, thermal or chemical stimuli, and the similarity of the response was remarkable. In a paper devoted to hemoglobinuria and urticaria from cold, Harris, Lewis and Vaughan[13] speak of urticaria as due to the liberation of histamine-like substances already present in the cutaneous cells and refer to the mechanism of an urticarial lesion as involving an increased permeability of the cell walls brought about by injury, or by other, and sometimes more physiologic types of interference. They state that the physiologic contents of the cells of the skin become liberated in the tissue spaces owing to increased permeability of the cell walls (comparable to what happens in the case of red blood cells in hemaglobinuria) and this release of a normal cell constituent is responsible for the cutaneous vascular reaction that follows.

In three cases of urticaria from cold, success was obtained in passive transfer in two cases, and this was held as main evidence for the presence of a dermolysin. Harris[14] later states "transference tests have yielded results that suggest that a toxic body is circulating in the blood and that whatever its nature and origin it acts by producing a definite skin reaction, known as spontaneous urticaria." Lewis[15] speaks of the vasodilatation in the skin occurring in response to cold as a result of the release of H-substance awakening an axon reflex.

Rackemann[16] speaks of the state of allergy as characterized by a diminished resistance to histamine-like substances as an attractive suggestion finding support in certain experiments, and he takes the view that a nonspecific H-substance normally present in skin cells is released by an injury caused by a specific antibody-antigen reaction taking place on the cell's surface. It is clear therefore that Lewis' views on the release of H-substance as an important factor in the development of the urticarial reaction has received very general acceptance. Recently, however, Rous and Gilding[17] question whether local vasodilatations after different tissue injuries are referable to a single cause. They found that the impulse to vascular contraction

arising in skin from which the circulation has been cut off prevails over that responsible for local vasodilatation after mechanical injury, with the result that the bloodless blanchings known as Bier's spots develop in regions where previously this vasodilatation had reigned. On the other hand the least quantity of histamine which is capable of causing local vasodilatation renders the vessels involved refractory to the contractile influence. They conclude that the results raise doubts concerning the validity of the hypothesis referring all local vasodilatations to the action of a single chemical substance or set of substances (H-substance), liberated within the tissues.

SUMMARY

Urticaria solaris is a rare form of physical allergy elaborated by Duke as a specific variety of contact reaction. A case is described with general as well as local manifestations, and several cases are cited from literature. The evidence for and against the concept of the release of histamine-like (H-substance) as the responsible factor in the production of the urticarial reaction is discussed.

Fundamental factors in light-sensitivity are unknown. Hematoporphyrinemia has been suspected but never found; experimentally it leads to light-sensitivity. The majority of recorded cases have occurred in women, and in three the disorder seemed related to disturbances in menstrual function.

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Society Proceedings

THE ASSOCIATION FOR THE STUDY OF ALLERGY

NINTH ANNUAL MEETING, PHILADELPHIA, PA., JUNE 8 AND 9, 1931

(CONTINUED)

Maximum Dosage in Pollen Therapy. GRAFTON TYLER BROWN, WASHINGTON, D. C. (For original article, see page 180.)

The Perennial Treatment of Seasonal Hay Fever. AARON BROWN, NEW YORK. (For original article, see page 113.)

DISCUSSION

DR. GEORGE PINESS, LOS ANGELES.—I wish to take issue with Dr. Brown that he is able to obtain an extract giving better than 3 per cent. It has been our experience that attempting extraction by many methods, such as thawing and freezing, grinding the pollen in a pebble mill and then extracting it, extracting by the ordinary methods in buffered salt or by allowing it to stand from two hours to several days, we were unable to get greater concentration than 2 per cent. Another point of interest is the small number of failures obtained by the essayist. It is rather a sad commentary on those of us who are devoting all our time to the field of allergy and have as many failures as we have reported. The collected cases of several workers show a total average of only 33 per cent who obtained complete relief, with 60-odd per cent obtaining practically complete relief, and the remainder being failures.

DR. LEON UNGER, CHICAGO.—In regard to Dr. Grafton Tyler Brown's paper, I admire his courage and I want to hear more from him next year and the year after as to his results with this 10 per cent and 12½ per cent solution. I do not think we should be too critical of him. I think he is perfectly justified in trying it out, and I do not think that any of us who have not used as strong solutions as he uses, has any right to criticize his results.

I have never tried anything stronger than 1 per cent, so I do not believe that I am in a position to talk about his results. At the same time, he says he starts his treatment six months ahead and gives at weekly intervals 26 injections to get up to 10 per cent. That seems to be a little too rapid advancement of doses. We give 25 to 40 injections to our patients, and it is rather difficult to get them up to half a c.c. of 1 per cent solution and to get them to 10 per cent in 26 weeks seems to me rather rapid, and I should be afraid of constitutional reactions.

I was very much interested in Dr. Aaron Brown's paper. We have been trying perennial treatment for the last two or three years, and I do not know whether our results are better with perennial treatment than with preseasonal treatment. This year we are dividing our group into two classes and we are testing them out.

It seems to me that injecting at intervals of four weeks as Dr. Brown does is open to danger of constitutional reactions. I should like to know from Dr. Aaron Brown, in figures, how much better his perennial treatment results are than those from preseasonal treatments.

DR. A. CLARKE, PHILADELPHIA.—We have been using Dr. Aaron Brown's method in a few cases for a number of years, and I want to say that we believe

that it will do all Dr. Brown says for it. One point I think should be brought out here and that is that if you have not been successful in your original treatment of hay fever, there is no point in continuing such a treatment over the next year. We always advise the patient to start over again the following year in the hope that we shall be able to add some other pollen or make some change in the treatment so as to get a more nearly perfect result, but in those who get the perfect or almost perfect results the year-round treatment should be suggested.

The greatest difficulty is to get patients to come in once a month. Fifty per cent of people who start, slip up somewhere along the line so that out of 20 or 30 patients, only about 10 have faithfully followed treatment throughout the winter.

Then there is another complication in an occasional person's becoming more sensitive on the once-a-month treatment. Such patients, for no reason at all, will have a constitutional reaction when given the same dose that they tolerated the month before.

In one patient I had to stop this treatment because on three successive months, although I reduced the dose over what I gave the month before, he had a constitutional reaction. His last dose was in February, and he has gone through the best part of this early grass season and has had less difficulty than he had with either the prophylactic or the year-round treatment.

I think the method is well worth further trial. If it does nothing else, it will decrease the terrible load we all have to carry during the months of June and July.

DR. C. ULYSSES MOORE, PORTLAND, ORE.—One thing which I should like to ask the Doctors Brown is whether they have used the seasonal treatment on the basis that is now being used in St. Mary's Hospital in London. An article by Dr. John Freeman on "rush" inoculation published in the *Lancet* for April 5, 1930, explains his technic. Dr. Freeman said that he believes that their laboratory deserves the blame for starting the preseasonal treatment and the weekly method of giving treatments. He says the reason that his first paper, published twenty years ago, "stated once a week is because we had our clinic once a week, so therefore we had our patients come in once a week. The whole world has since followed that weekly method." He says, "Now we wait until the season begins and then give what we call the 'rush treatment.'" On treatment days he starts his work in the hospital at five o'clock in the morning. The patient receives seven properly graduated doses daily at intervals of two hours. In three days he has received what would ordinarily have taken many weeks. According to his reports, both written and verbal, the patient leaves the hospital very much improved.

DR. LOUIS TUFT, PHILADELPHIA.—I should like to ask Dr. Aaron Brown whether after he gets his patients to the maximum preseasonal dosage, he attempts to prolong the interval beyond that of a month. I have attempted this in four patients so that they can now take the maximum dose, at an interval of two and one-half months without any difficulty, and all of these patients over a period of two years have never had a constitutional reaction. I just wonder what the longest interval Dr. Brown has allowed between treatments.

DR. J. H. BLACK, DALLAS.—We have had some experience in the last year and a half with Dr. Aaron Brown's method and felt it was a definite advance with many of our patients. They were distinctly superior to the results we got with some of the patients with preseasonal treatment.

As to Dr. Grafton Tyler Brown's extracts, several years ago we were using routinely 5 per cent extracts made up in the same manner he suggested and felt we might do better with 10 per cent and did it on the same basis and found we were not doing any better. I have been a ragweed hay fever patient myself. I tried substituting the 10 per cent in the same dose and got by with it in the same

manner I did with the 5 per cent, so I went back and made extracts from 1 per cent to 10 per cent and put them into my nose to see the minimum amount of each which would produce the effect. It happens, in my nose at least, that I have a threshold which does not vary from day to day. We found that the amount of allergen from the pollen increased to a little over 2 per cent and then did not increase at all. A 5 or 10 per cent extract was no more effective in my nose than a 2 per cent.

DR. ZELLA WHITE STEWART, IOWA CITY.—I have been using the perennial treatment of hay fever for the last eleven years, and presented a paper on this subject at the third annual meeting of the Society at Dallas in 1926.

I find that patients never lose their tolerance when once it is built up, as they do between seasons with the preseasonal method of treatment. All my patients take their own treatment. This may seem open to criticism, but there is no danger of constitutional reactions if the treatments are taken carefully. Each begins with a weak solution, increasing the strength very slowly, and taking injections every other day, or every third day until he has reached his maximum dose. This is repeated twice weekly until August 15, when one-half the maximum dose is given, until frost. One then takes the maximum dose once in two weeks until the following July, when the injections are given twice weekly. After two years the time between injections is extended to one or two months until July. This is continued over a period of five years or until they have remained free from symptoms for two years. There is progressive improvement from year to year. The first year one may expect at least 35 per cent improvement, and in many cases the report is 75 per cent to 90 per cent improvement. The best results are not obtained from treatment unless the other things to which a patient is sensitive are eliminated during the hay fever season, even though they may be tolerated during the rest of the year.

DR. HARRY L. HUBER, CHICAGO.—I have never been able to get very much of a difference in the extracts of pollen above 2½ per cent. A 5 per cent or 10 per cent extract does not seem to be very much different from a 2 or 3 per cent extract.

Dr. Aaron Brown's method of continuous treatment I have been using for some years, and the results as I am seeing them now are quite satisfactory. As he says, it can be said they are at least no worse than the others and many of my patients get as good or better results. I know that the skin tests diminish appreciably during such treatment.

DR. WARREN T. VAUGHAN, RICHMOND, VA.—My experiences with perennial desensitization have been very satisfying to me. This last year I have gone over a relatively small number of cases who have been seen and treated by me in the office and treatment has been carried on throughout under my supervision, leaving out cases that have been referred, where my diagnosis has been made and another doctor has gone ahead with treatment.

In the vicinity of Richmond I have to run up to ½ to 1 c.c. of a 2 per cent concentration. From that I drop back to 0.1 c.c. of a 2 per cent concentration for maintenance. I give the treatment every two weeks through the year, comparing the results. Of the perennial group only two had symptoms to amount to anything.

DR. W. W. DUKE, KANSAS CITY, MO.—I think when we evaluate any method of treatment, we have to consider the pollen content of the air in the district in which it is used. In Dr. Brown's district the pollen content of the air is enormously lower than in Kansas City. Our pollen counts are enormous. This is true in general in the Middle West. I think also our advice to patients modifies the result of therapy, that is advice concerning pollen avoidance.

I should like to ask Dr. Brown who is the originator of the method of perennial treatment? I think the history of it should be reviewed carefully because I am convinced that it is the coming method of treatment. The first I heard of this method was from Dr. Zella Stewart at the Dallas meeting of the American Medical Association in 1926. I have followed Dr. Stewart's advice for several years concerning perennial treatment at monthly intervals. I believe if we give the monthly treatments and especially if we give the doses at two or three month intervals we should use ephedrine in with our pollen mixture and also adrenalin.

DR. M. MURRAY PESHKIN, NEW YORK CITY.—May I ask a question? Does not the statistical record reported thus far on perennial treatment of pollen allergy indicate that only certain groups of cases were selected for this type of treatment?

DR. GRAFTON TYLER BROWN.—This is a good deal to cover in only three minutes, but I shall at least touch upon all of the high spots in the discussion.

Dr. Piness wants to know whether I make my own extracts, and if I macerate the pollen. I prepare all of the extracts myself, and have never tried macerating the pollen. Seasonal hay fever victims develop all of their symptoms from the inhalation of whole pollen, so I see no reason for attempting to improve on nature by grinding the pollen.

As for its being impossible to make pollen extracts stronger than 2 per cent, I would call attention to the fact that Dr. Kahn and also Dr. Duke have been using 5 per cent extracts for a number of years. Furthermore, Dr. Coca, whose opinion we all respect, prepares 3 per cent stock pollen extracts. If he were not convinced that 3 per cent extracts are stronger than 2 per cent, why would he waste the extra pollen?

I wish to thank Dr. Unger for his gracious remarks. My present method of treating pollen hay fever has been developed through a process of evolution, as I had no preformed opinions in the matter. In former years, along with my successful and partially successful results in the treatment of seasonal hay fever, I encountered some complete failures. These failures have been the "bugbear" of every one treating hay fever, for it is certainly discouraging to both patient and physician when the patient has hay fever as badly as ever, following a lengthy course of preseasonal injections. As the diagnoses in these cases were plainly correct, I felt the need for improvement in the generally accepted method of treatment. In the absence of constitutional reactions following the injections, I thought that the failures must be due to insufficient dosage. As proof of the correctness of this view, I was able to take my failures of one season and convert them into successes the next year, merely by giving them much stronger preseasonal doses. When using 1, 2, or 3 per cent extracts, I found myself limited as to maximum dosage by the large bulk of fluid necessary. It is usually impractical to inject much more than 1 c.c. of glycerine extract at one time, so the logical thing to do was to prepare more concentrated extracts.

I am convinced from innumerable tests that my 10 per cent pollen extracts are stronger than either 2 per cent or 5 per cent extracts. Some patients under treatment will become skin negative to 2 and 5 per cent extracts, yet will still react to 6 or 10 per cent extracts. My reason for using both 6 and 10 per cent extracts at the present time, is that during 1928 and 1929 I was preparing my pollen extracts in a concentration of 6 per cent, but since then I have been making all of them 10 per cent.

Dr. Unger said that if I start a patient's treatment six months before season, and reach a dose of 60,000 pollen units by the beginning of the season, I am doing a good job. I thoroughly agree with him, for only rarely can this be accomplished with the treatments on a weekly basis. Even though the maximum

dose is not reached before season, however, a satisfactory seasonal result is usually obtained. Whatever dose is attained just before season, is repeated throughout the season. Following the season, I continue the treatments perennially at weekly intervals, in increasing doses until a maximum is reached, striving all the time to wipe out the skin reactions. For those patients who will not take perennial treatment, each year's course of preseasonal injections should be regulated so as to attain a stronger preseasonal dose than was reached the year before.

Dr. Moore asked if I had tried Dr. Freeman's coseasonal method of treatment. I have not, but thoroughly agree with Dr. Vaughan and others as to the efficacy of coseasonal treatment, using small, carefully regulated, and frequently repeated doses of the specific pollen extract.

I think I have already answered Dr. Black's point about 10 per cent extracts being stronger than 5 per cent. I might also add that if you use a uniform technic for extraction, you can judge the concentration of an extract by its depth of color. Although the coloring matter in pollen is not the antigenic principle, nevertheless, with a uniform method of extraction, the intensity of color of a pollen extract runs parallel to the pollen content. When dilutions of a concentrated pollen extract are prepared, the more they are diluted, the paler they become, until they get to be the color of water. If a 2 per cent pollen extract is held up to the light, side by side with a 6 or a 10 per cent extract prepared in the same way, it may readily be seen that the latter contains more pollen, and it has a correspondingly greater "kick."

If any one doubts the possibility of giving 60,000 to 100,000 pollen units at a single dose, I would refer him to our distinguished President, Dr. Balyeat, or to other members of this Society, who have seen such doses administered during visits to my office, not only to strong, husky men, but also to frail women and children, with no constitutional reactions, and without the use of tourniquets, ephedrine, or epinephrine.

Dr. Duke brought up the point that we have lower pollen counts in the District of Columbia than in other places. Although the majority of my patients are from the District of Columbia, some of them treated by this method have been from Virginia, New Jersey, Rhode Island, Oklahoma, Texas, and other distant states. These patients from other states have gone through the entire pollen season in their own communities just as free of symptoms as those residing in Washington.

I do not ask you to believe all this, just because I say it is so, but do not misjudge the method until you have tried it. When my paper is published, read it carefully with an open mind, then give the method a faithful trial, and I think that you will be able to convert your former failures into successes. You will then be in a position where you can almost assure the hay fever patient of a satisfactory season.

DR. RAY M. BALYEAT, OKLAHOMA CITY.—Dr. Brown has already closed the discussion but I would say that I have always assumed that the color of my extracts was due to the oil instead of the antigenic material.

DR. AARON BROWN.—As far as the figures of results are concerned, I want to say that in the perennial treatment, applied to those getting 75 per cent or better results the first season (preseasonal), my results in perennial treatment are at least 10 per cent better. As far as the interval is concerned, I have often given patients injections six or eight weeks apart. To one patient I gave an injection at the end of a three and a half month period and that same patient experimentally took his maximum dose of timothy, 0.035 mg. N per c.c., after a lapse of five months, without getting a constitutional reaction. Generally speaking, however, we should plan to give injections, with a month as the maximum time interval.

In answer to the question on the rapid desensitization method, I want to say that I have had no experience with it.

Regarding the question of priority, my perennial work started in 1920, and from that time on, the men at the New York Hospital have been familiar with the work done with the patients I carried along both at the hospital and at the office.

I hope more physicians will try the method. I am sure if you exclude all other associated sensitivities, such as orris root, feathers, etc., and use the pollens that are indicated, your results will be most gratifying with the perennial treatment, and I agree with Dr. Duke that all of us will be using this method of treatment in the future.

Emanations of Flies as Exciting Causes of Allergic Coryza and Asthma. III. Hypersensitiveness to Moths and Butterflies (Lepidoptera). S. J. PARLATO, BUFFALO. (For original article, see page 125.)

DISCUSSION

MR. O. C. DURHAM, NORTH CHICAGO.—I shall take a moment to say that on most of our national series of slides I do not find a great many butterfly and moth scales. I have never taken the trouble to count them or make a record, but slides from Florida often show a great many, considerably more than there are pollens. I am planning with Dr. Parlato to report all butterfly and moth emanations on the U. S. Weather Bureau slides this year.

DR. HARRY S. BERNTON, WASHINGTON.—I desire to congratulate Dr. Parlato. His contribution is a very valuable one. I should like to ask Dr. Parlato if he has had experience with the wings of the ordinary house fly which is more or less universally found.

DR. W. W. DUKE, KANSAS CITY, MO.—I want to congratulate Dr. Parlato on his work. I have tested patients routinely for fly sensitiveness and I have found several positive cases. We have enormous swarms of these flies in Kansas City. They can be found in great numbers around bright lights. I had one case that gave a complete clinical relief after three treatments with fly extract.

DR. KARL D. FIGLEY, TOLEDO.—I want to congratulate Dr. Parlato on this splendid presentation. I think that this work is opening up a very large field with regard to the discovery of new allergens, and I wish to emphasize, as Dr. Duke has done, that these flies are not confined to the lake districts, but are found all over the world, around large rivers and streams. In fact, in Izaac Walton's book *The Compleat Angler*, he describes the flies, which, of course, he discovered in England.

I should like to ask Dr. Parlato if he has made comparative tests on his caddis fly sensitive patients with May fly extract? I have had the opportunity to test out one patient with both, and the patient reacted to the May fly, but not to the caddis fly.

DR. PARLATO.—I want to express my appreciation for the complimentary remarks made by those who discussed my paper. I am very much encouraged by the favorable criticisms which have been expressed here, but the fact that I did not hear much adverse criticism makes me afraid and cautious. It is my hope that you will undertake to study and observe these flies in your respective cities. In this way, we can hope for some collaboration of my work. I shall be glad to furnish some extract of these flies upon request.

Dr. Bernton asked about the house fly. Naturally I am extending the studies to include all the common flies. I am not giving any further consideration to the house fly, as I found that it did not produce any emanations like the sand fly and

moths. The wing itself is nothing but a membranous structure similar to that of the May fly. You have heard, as a matter of fact, that the feet of the house fly have hair, but those are more for tactile purposes than the kind of hair we are speaking of. I doubt whether they are capable of causing allergic symptoms through inhalation. It is possible that immediate contact on the skin could cause symptoms.

I appreciate Dr. Duke's encouraging efforts to cooperate with my work. His experience, I am sure, can be duplicated by any member who will look for these flies during this summer. In about two or three weeks, you will see them just as sure as you will see grass pollen in the air.

Dr. Figley asked about the May fly. I think it was a year ago I asked him for some of his May fly extract. Naturally, I was very much interested in determining whether some of the people in Buffalo could be sensitive to the May fly, as they are found in great numbers along with sand flies and moths. These three flies are found very much together. Their life habits are the same. They are attracted to electric lights. You see them on the streets, on the cars and on your clothes as you walk along the streets of Buffalo. I have prepared a paper on the May fly which I hope to publish in the near future. Briefly, I wish to say this much, that my repeated examinations of specimens of May flies show that there are no emanations such as we see coming from the *trichoptera* or *lepidoptera*. Their wings are wide and big in proportion to their body but there are no emanations.

Dr. Figley also spoke of the pellicle of the May fly as it leaves the water. I have looked for this pellicle near the water and inland. I expected to find it and did not. It is quite possible that I have overlooked it.

I tested, I think, a series of about 200 patients with his extract, and I found one patient who gave a good skin reaction but it was not confirmed by the eye test. Taking some of the wing of the May fly and putting it in the eye did not give a positive reaction. I also tested all those cases which I considered sand fly positive. There were none which reacted to May fly.

The Incidence and Rôle of Paranasal Sinus Disease in Hay Fever.

RICHARD A. KERN AND J. C. DONNELLY, PHILADELPHIA. (For original article, see page 172.)

DISCUSSION

DR. LEON UNGER, CHICAGO.—Were those x-ray pictures taken during the hay fever season or preceding it?

DR. DONNELLY.—Several months before.

DR. GEORGE PINESS, LOS ANGELES.—I was very glad to hear this paper because it confirms the opinion expressed by myself and workers in about 1924. At that time we contended that sinus disease as a rule plays a very small part in the average hay fever individual, that when sinusitis did occur it was usually secondary to the hay fever condition, and that other pathologic conditions such as nasal polypi, were a secondary factor, and all such conditions should be removed or treated to prevent further extension of the respiratory infection. I should like to ask Dr. Donnelly the technic of his x-ray studies in these cases and whether or not they were restudied from an x-ray standpoint following the hay fever season.

DR. KERN.—In regard to the matter of x-ray, that was done by what we feel is perhaps the most complete sinus x-ray technic that we know of. I think that is why we get such a high incidence of positives, 70-odd per cent in normal individuals. I must say in explanation of that, that those are all individuals living in or around Philadelphia where sinus disease is perhaps more prevalent than anywhere else in the country.

The method of testing was in almost all instances by the scratch method. As to the number of positives, if you got the impression that our pollen cases had negative reactions to pollens, the slide apparently was not quite clear. Of our 75 cases, only two did not give clear-cut positive reactions to pollen.

Studies in Asthma. XIV. Bronchoscopy in Asthma. FRANCIS L. WEILLE, M.D., BOSTON, MASS. (Abstract.)

In order to determine the mechanism by which bronchoscopy gives benefit to some patients with asthma and perhaps to define the type of patient suitable for this form of therapy, a study has been made of 15 patients observed in the Anaphylaxis Clinic of the Massachusetts General Hospital and in the Bronchoscopic Clinic of the Massachusetts Eye and Ear Infirmary. These 15 patients were examined and treated through the bronchoscope, and all of them have been followed for periods of six months to two years. The follow-up period is short, but it seems worth while to report the results so far.

This report deals with the findings at the time of examination and emphasizes the importance of the character of any exudate in the tracheobronchial tree, particularly that which is so tenacious that it clings firmly to mucous membrane, despite cough. A corollary of this point places such secretion in the rôle of a foreign body, removal of which, even in a small quantity, would be beneficial. An attempt has been made to correlate the clinical progress of the patient with any changes observed through the bronchoscope.

The theories of the mechanism of the asthmatic attack are the familiar conceptions of spasm of the smooth muscle of the bronchioles and of edema of the mucous membrane. From the present study a third possible mechanism is suggested: namely, the partial occlusion of large or small bronchi by a peculiarly characteristic sticky, highly tenacious mucoid secretion. Jackson has described the different types of valve-like action which viscid bronchial secretions may produce. The glue-like secretion appears to act as a partially efficient check valve to the particular portion of the lung distal to it, allowing air to enter the lung during the inspiratory dilatation of the bronchi but trapping the air distal to the point of obstruction upon expiratory contraction of the lower air passages. Patients with these findings may be described as having "exudative" asthma; it is felt that to this type insufficient attention has been paid in the past.

The object of bronchoscopy is the mechanical cleansing of large and small bronchi.

A great many patients with asthma give the history of having a severe attack which terminates when the patient is able to "raise" quantities of thick secretion by coughing. In general, patients who gave such a history were regarded as favorable subjects for bronchoscopy. Bronchoscopic therapy was not advised as "a last resort."

Patients having bronchiectasis were regarded as favorable subjects simply for drainage of ordinary pus from the bronchial tree.

All of the 15 cases reported have been followed for from six months to two years. Four received no benefit. One patient described himself as "cured" when heard from nineteen months after treatment. Another was practically "cured" a year after treatment. A third was "cured" for a period of fifteen months with the exception of a single attack. In a fourth patient the procedure was "life-saving." In the remaining seven patients there was marked relief which lasted for from two weeks to seven months following each bronchoscopic treatment.

The most typical single pathologic finding in the group of cases was the presence of thick, viscid, extremely tenacious secretion in the tracheobronchial tree. The present study suggests that the character and the distribution of such secretion are of more importance than the amount, inasmuch as a very small quantity, not dislodged by coughing, can grossly obstruct several large bronchi. Cases having an entire absence of tracheobronchial secretion have been found to receive no benefit from bronchoscopy.

The majority of the cases showed more than one organism at each examination. The diversity of the organisms identified enables one to conclude that no single bacterium is characteristic. The wide diversity of the bacterial flora suggests that all the organisms found are secondary factors.

Eosinophiles were not found to be remarkable in the smears. So far the cilia appear normal in our cases.

CONCLUSIONS

1. "Exudative" asthma describes a symptom, not a disease, and means that there is a greater amount of secretion than is normal in the tracheobronchial tree. Such asthma may be of any type—intrinsic, extrinsic, or unclassified.

2. Insufficient attention has been paid to this condition and its relief by means of bronchoscopy.

3. Seventy-three per cent of the patients reported in the present study have been benefited.

4. In the cases experiencing relief, inspissated sticky secretion clinging to the bronchial mucous membrane is the most interesting pathologic finding.

5. The bacteria isolated from the tracheobronchial tree are probably secondary invaders.

6. The cilia appear to be normal anatomically and physiologically.

7. The mechanism through which the patients reported have obtained relief is probably mechanical. Mucous membrane cocainization, trauma, medullary reflexes, mechanical stretching of bronchi, etc., may be less important factors.

8. Bronchiectasis in asthma may be an end stage of "exudative" asthma. The present study suggests that bronchiectatic changes may be prevented by the use of bronchoscopic therapy.

DISCUSSION

DR. GEORGE L. WALDBOTT, DETROIT.—Some time ago Dr. W. A. Hudson of Detroit did bronchoscopies on a number of my asthmatic patients in order to investigate the pathology of the bronchi in allergic bronchitis, a condition on which I have discussed three years ago before this Society. Our cases were of course different from the ones just described. We had the very earliest manifestations of true allergic asthma with no other symptoms than the dry nonproductive bronchitis resembling pertussis. In these cases comparatively little mucus was found. Small petechial hemorrhages and swelling and hyperemia of the mucosa, occasionally some yellowish, whitish secretion were the characteristic findings. Bronchospasm was also very marked.

On examining and culturing the mucus we found lymphocytes and eosinophiles but very few bacteria and few neutrophiles. In distinction to these cases, in the farther advanced patients the neutrophiles and positive cultures were more prevalent. Dr. Hudson's therapeutic results from the elimination of mucus were questionable, although occasionally patients showed a tendency toward improvement.

DR. HARRY L. HUBER, CHICAGO.—Some patients have quite a lot of exudation. The secretions tend in some patients to collect in the bronchi, and the muscle spasm, in addition to the secretion, is the thing that causes the trouble.

Was there a single bronchoscopic examination made, and did the removal of these mucous plugs a single time cause a patient to have entire relief from the symptom over a period of several days or weeks?

The pathologic studies of the lung tissue from the asthmatic will show areas of atelectasis. This may be interpreted as meaning that at some time or other the bronchus was totally occluded by a mucous plug that was never expelled and the portion of the lung from which this bronchus leads has become an atelectatic area.

DR. A. TRASOFF, PHILADELPHIA.—Any one who is treating asthmatics especially of long duration realizes the importance of bronchiectasis as an added difficulty to the patient as well as to the physician. These patients expectorate large quantities of purulent material and usually with great difficulty.

The bronchoscopist is of great help in such cases. However, bronchoscopy is frequently unnecessary, and relief can be given the patient by a more simple method. In a few cases of the infectious type of asthma treated by me in the allergic clinic, Mt. Sinai Hospital, Philadelphia, who presented clinical and x-ray evidences of bronchiectasis, I was able to give the patient great relief by the administration of lipiodol into the affected lung.

The technic is very simple. The throat and the posterior pharynx are cocainized with a 10 per cent solution of cocaine hydrochloride until the swallowing reflex is abolished. By the means of laryngeal cannula attached Luer syringe about 20 c.c. of 40 per cent lipiodol in olive oil is introduced into the affected lung. Within twenty-four hours or so the patient brings up a great deal of pus and experiences great relief. This procedure may be repeated once weekly for a few weeks.

DR. RICHARD A. KERN, PHILADELPHIA.—I should like to say concerning the use of lipiodol that it is a routine procedure in the bronchoscopy department in the University of Pennsylvania to remove through the bronchoscope as much of the lipiodol as possible. One reason for doing this is that we are dealing with a group of patients in whom idiosynerasies to drugs are extremely common, and among

these iodine is perhaps the commonest. I have seen amazing and alarming reactions follow the use of lipiodol, and had it not been removed immediately, there might have been tragic results. So it might be wise, if you are going to use lipiodol in the manner just referred to, to be absolutely sure you are dealing with a patient who is not hyper-reactive, if I may use that term, to the iodides.

DR. L. WEILLE.—Regarding the question as to the number of bronchoscopies in the various cases, the number varied from a single bronchoscopy in eight of the cases to two to eleven bronchoscopies in the remaining patients. In the patients receiving temporary benefit, the improvement lasted from two weeks to seven months following each bronchoscopy. Three of the patients reported themselves as "cured" of asthma during follow-up periods varying from a year to nineteen months at which time these patients were last seen.

It is indeed true that sticky tenacious secretion in the lower air passages is troublesome to asthma patients. As a matter of fact it was finding at autopsy of an asthmatic patient that the tracheobronchial tree was entirely filled with such secretion that convinced Dr. Rackemann of the value of bronchoscopic therapy in certain asthmatic patients. Two weeks after this autopsy a second asthmatic patient appeared to have the lower respiratory tract filled with secretion in which the patient seemed to be drowning and bronchoscopy proved this to be the case. It was felt that this bronchoscopy saved the patient's life.

It should be emphasized that the type and distribution of the secretion are more important than the amount of the exudate and that the removal of a small amount of thick, highly tenacious secretion may be of great benefit to some patients.

Congenital Protein Hypersensitiveness. Protein Hypersensitiveness Transmitted From Allergic Mother to Child. BRET RATNER AND JANET E. GREENBURGH, NEW YORK. (For original article, see page 149.)

DISCUSSION

DR. HARRY L. HUBER, CHICAGO.—I have one patient, whose mother ate peanuts in large quantities during her pregnancy, the child was never nursed, and within a short time after birth gave marked skin reactions when touched with a peanut.

DR. ALBERT H. ROWE, OAKLAND, CALIF.—We have followed Dr. Ratner's work with the greatest interest and feel indebted to him for his illuminating insight into this problem in which he is interested and to which he has added so much.

We find histories of families where there is a definite egg sensitization through two, three, and four generations. Such reports have been in the literature for a number of years, and I am sure all of us in carefully taking our histories from the point of view of food allergy run into them ourselves.

It is my opinion that there is transmitted also a definite tendency to the establishment of a specific type of sensitization. People who are sensitive to pollen may transmit the tendency to develop this type of allergy to their offspring. I do not know whether it is an actual transmission in the same sense of the word that Dr. Ratner has described this afternoon. People who are food-sensitive may not actually have offspring who are sensitive to the same foods, but there seems to be a tendency to transmit the ability to become sensitized to foods.

DR. C. ULYSSES MOORE, PORTLAND, ORE.—I, too, want to thank Dr. Ratner for his illuminating paper. I should like to ask him whether he has found any cases that seem to be transmitted through the paternal side of the family and, if so, how he would explain that.

In testing our eczema cases in children, we have frequently found that there would be such things as duck, turkey, goose, and chicken that the child would be sensitive to and the mother sensitive to three out of the four, and perhaps the father sensitive to two out of the four. In one case we tested the grandchildren, then the parents, and the maternal grandfather, and we found in the same series that the paternal grandfather had a reaction to three out of those four foods. We did not test his wife, but there were no signs of any trouble on that side of the house.

DR. GEORGE PINESS, LOS ANGELES.—I think Dr. Ratner should be congratulated on this timely piece of work presented to the Society this morning, in that he brings out very forcibly a conclusion reached by us but differed in by Dr. Coca and his workers, that anaphylaxis and allergy are the same and can be used synonymously in talking about conditions such as hay fever, asthma, etc., that we see in our daily work, and that atopens and allergens are similar terms both having the same meaning and usefulness.

DR. RICHARD A. KERN, PHILADELPHIA.—Dr. Piness has stated my question as to the possible explanation of the mechanism of transmission of this thing by the male. I suppose now since viosterol is being given to every infant, we shall have to exclude peanuts from the diets of all pregnant mothers.

DR. RATNER.—In answer to Dr. Moore, I should like to state that it is very difficult to evaluate the question of heredity in a history that is casually presented. Careful scrutiny of all the essential details of such a history is essential before an opinion can be voiced as to whether there is an hereditary basis or not. There is no question at all that allergy may be present in the male as well as in the female because I believe that allergy may be acquired, but to link up the hereditary transmission through the male is difficult to conceive.

What I wish to bring out in this study is that sensitization may be acquired in utero in the same way that an individual may become sensitized through inhalation, through ingestion or as the result of an injection. Sensitization in utero therefore is merely one manner in which an individual may acquire his hypersensitiveness.

The Mechanism of Human Anaphylaxis. GEORGE L. WALDBOTT, M.D., DETROIT, MICH.

(Abstract)

An analysis of eight cases of death from anaphylactic shock and a study of anaphylactic reactions from pollen injections form the basis of this paper.

The factors involved in the production of shock are first, individual sensitiveness, either inherited or acquired; second, rate of absorption; third, dose of antigen. The rate of absorption depends upon whether the antigen is given strictly intramuscularly or it is injected accidentally into or near a punctured vein, and then seeps back into the blood stream.

The characteristic symptoms of human anaphylactic shock are spasm of smooth musculature, especially of the bronchi and dilatation of capillaries (wheal). Clinical observation suggests that this is produced by the action of a chemical substance which is generated as the result of an overdose of antigen for which not sufficient antibody is being produced.

DISCUSSION

DR. BRET RATNER, NEW YORK CITY.—Dr. Waldbott's paper is very interesting but, I believe, in a sense misleading. In the evaluation of the mechanism of human anaphylaxis he does not take into account the fact that we have shown that death due to an initial injection of horse serum is not necessarily the result of previous horse serum injections, but may result from a natural sensitization of the common globulins found in horse dander and horse serum. The majority of cases of anaphylactic death due to serum occur in those individuals who are sensitive to horse dander.

We were able to produce asthma in guinea pigs experimentally through the inhalation of horse dander and kill them with an initial injection of diphtheria antitoxin. Dr. Waldbott's statement that 6 c.c. is the amount required to kill a guinea pig is far from correct.

DR. WALDBOTT.—Lewis made the statement.

DR. RATNER.—It requires a minute amount of antigen to kill a guinea pig, and according to your dose it would require an exceedingly large amount to kill a human being. But such is not the case, for individuals have died from very small amounts of injections of foreign protein. Lamson reported a case where 1 c.c. of pollen injection was sufficient to kill his patient. Individuals have died from small prophylactic injections of antitoxin. I doubt whether Julian Lewis has made this statement. You report Dean's case as evidence for certain factors which you believe are not purely anaphylactic. I should like to state that this case is one of human anaphylaxis which resembles the canine type of anaphylactic death. This accounts for the tremendous fall in systemic blood pressure.

DR. WALDBOTT.—I did not subscribe to his theory.

DR. RATNER.—It is a remarkable case but rather unusual, for the typical type of anaphylactic death occurring in human beings resembles what we encounter in the guinea pig, namely a complete bronchial spasm. It seems to me that to invoke the parasympathetic system and the thymus is to disregard the great advances that have been made in specific hypersensitiveness, for if an individual is sensitive to horse serum and dies only as a result of a specific serum, why is it necessary to invoke other factors to explain such anaphylactic death? I believe that we are very fortunate in the field of allergy to have a subject which is specific, that is a hypersensitiveness which depends on a particular form of sensitization which may result in anaphylactic shock only as a result of a specific injection of that specific substance and none other.

The newer work of Avery and Landsteiner on haptens does bring out factors that have to be considered, for we did not know in the past that carbohydrate substances could produce anaphylaxis. But these carbohydrate substances must be in combination with proteins. The full significance of this new work is not yet fully understood, but it does not militate against the pure antigenic specificity of anaphylactic shock.

DR. WALDBOTT.—I am well aware of the fact that very small amounts of horse serum may occasionally produce animal shock. But as most workers agree, large sensitizing doses of serum produce shock much more promptly. The figure of 6 c.c. is considered by Lewis as the average dose of serum which kills the average guinea pig.

Dean's case report is probably one of the best descriptions of human anaphylactic shock. Because he followed it up with subsequent pathologic studies on dog anaphylaxis, he conveys the impression that his case resembles the dog type and

not the guinea pig type of anaphylaxis. I cannot conceive how a certain agent such as horse serum may produce a dog-type lesion with its typical liver necroses in one human being and the guinea pig type in another. As a matter of fact, both lesions were present in Dean's case. It is likely that the few subsequent investigators of human anaphylaxis may not have studied the liver so carefully as he did, or in their cases the lesions of the liver were not yet so far advanced as to produce noticeable changes. I did not subscribe to Dean's explanation of the cause of death, but merely quoted his idea from a bibliographical point of view.

Whether the eight cases reported by me were sensitized by a previous injection with horse serum or by exposure to horse hair, is difficult to determine. I know, however, that they gave no history of previous allergy, but had horse serum injections before, which made me feel that the previous injections of horse serum made them sensitive.

I would not have brought the question of thymus into the discussion had it not been for the fact that seven out of fifteen autopsy reports recorded in the literature showed enlarged thymus and lymphoid hyperplasia. In view of the debatability of this subject I did not render any opinion as to the significance of this fact.

I do not wish to comment on Avery's haptens and on the influence of sympathicotonus on anaphylactic shock. I merely mentioned these features as they appear to the clinician.

The Mechanism of an Asthmatic Attack in Chronic Allergic Asthma.

BERNHARD STEINBERG, TOLEDO. (For original article, see page 139.)

DISCUSSION

DR. M. MURRAY PESHKIN, NEW YORK CITY.—Does Dr. Steinberg mean to infer that the experiment of injecting gum tragacanth into the bronchial tree of a normal dog followed by lipiodol parallels the injection of lipiodol into the bronchial tree of a human being suffering with an attack of asthma ranging from ten hours to four days? In dealing with persons with chronic asthma have the pathologic changes in the bronchial tree and lungs been taken into consideration? Even in the absence of pathology, and before the injection of lipiodol during an acute attack of asthma, does not the duration of the attack itself mean anything?

DR. GEORGE PINESS, LOS ANGELES.—I do not believe Dr. Steinberg has proved his point that all these deaths are due to plugs of mucus formed in the bronchus in such a way as to produce death in the cases that are reported as occurring immediately following injections of antigen, serum, or what not. My own experience with the deaths in asthma this year—I have seen five cases of bronchial asthma deaths, in all of which postmortems have been performed. I was interested in noting that there were three definite, distinct types of pathology found in them; in one, the type described by Dr. Steinberg occurring in individuals who did not die suddenly, and in every instance they had morphine before the death; the second type occurring in individuals very suddenly, immediately following or within a few minutes' time of the injection of the pollen or serum that was given.

The case reported by Lamson is one I had the opportunity of seeing. It was an individual who got 0.1 c.c. of pollen antigen, one to fifty Bermuda grass, and that individual died within two minutes. It took just that length of time to walk from the doctor's office to the door, and there he died. That man's lungs showed absolutely no evidence of mucous plugging.

We have another type I have observed in the individual not truly the bronchial asthmatic, but who has a so-called asthmatic bronchitis with perhaps some bronchiectasis. In him we see a definite thickening of the bronchi with perhaps some

mucus also thick and tenacious, and I believe a great deal of that is postmortem change. I doubt whether that occurs during the attack, that is, I doubt that it becomes so thick and tenacious during the attack.

DR. MILTON B. COHEN, CLEVELAND.—I believe it is very important in a discussion of this sort to differentiate between two things. I do not think Dr. Steinberg referred to the acute deaths at all, but to the mechanism of the attack in chronic asthma.

DR. PINESS.—His attack is acute.

DR. COHEN.—Not the death following the injection.

DR. PINESS.—That same man has his asthma, the patient who died that Lamson reported, had it five or six years.

DR. COHEN.—I think we should get further if we would discuss the patients who had attacks of asthma and died in the prolonged attacks; certainly those cases do show these very tenacious plugs at autopsy.

I am inclined to agree with Dr. Steinberg that in the asthmatic seizure the symptoms are the result of the mechanical plugging of the bronchial tree with some ball valve mechanism or something of that sort responsible for trapping the air in the lung below the more or less plugged area, with the production of symptoms.

DR. BRET RATNER, NEW YORK CITY.—I think Dr. Steinberg's paper is of great interest, if only from one standpoint, that he intimated several times that the bronchiolar spasm has not been proved, but that mucous plugging of the bronchi has been proved.

DR. STEINBERG (interrupting).—No, I did not intimate that, neither said nor intimated it. I have stated the reasons. I shall discuss it later on.

DR. RATNER.—The point is this, that Dr. Steinberg has reported an end-result of a pathologic, physiologic condition, purely mechanical plugging of large bronchi producing atelectasis.

There certainly are two types of death in asthma. One is the true type of asthmatic death in which the individual dies within a minute or two. There is no question about those deaths being immediate, and I do not think that those deaths have all the pathology that Dr. Steinberg has shown. Those are acute anaphylactic deaths due to a definite bronchiolar constriction. The smooth muscles around the bronchi are not affected, but the smooth muscle in the terminal bronchiol is.

In the production of asthma in the guinea pig, we can take any part of the lung when the animal dies and sever it from its bronchial tree and it will remain ballooned. In every case, in other words, the bronchioles are contracted and the individual vesicles are filled with air. Large mucous plugs could not give this picture, and parts of lungs severed from a bronchial tree that was plugged would result in collapse rather than the distension which is seen in the lungs of true bronchiolar spasm.

DR. H. M. COBE.—I just want to raise one question and that is the relationship between bronchospasm and mucous plugging. I think that the agreement is pretty well established that with bronchospasm you get emphysema, but with total occlusion, as you get in mucous plugging, you get atelectasis. That, it seems to me, is the crux of the whole situation.

DR. HARRY L. HUBER, CHICAGO.—There is one type of disorder that has not been discussed at all and that is that of the patient with a fibrinous bronchitis. Some of these patients do not have typical asthmatic symptoms until they are ready to raise these fibrinous plugs.

I certainly agree with Dr. Piness that many of these patients who come to autopsy die because of the administration of codeine or morphine. These people are literally drowned in their own mucus. Their reflexes are gone and they are not able to raise any more mucus and consequently cannot get any more air. I should like to say a word of warning: Do not use morphine or codeine in the chronic asthmatic.

DR. STEINBERG.—I suppose I am allowed the usual three minutes to answer all these questions.

In regard to Dr. Peshkin's question, I do not believe it is material whether we are dealing with a dog or a normal or abnormal mucosa. Our purpose was to determine whether lipiodol will show a picture similar to that in the human when the bronchi are plugged.

Regarding the various questions raised, especially the one by Dr. Piness, I do not think Dr. Piness is very familiar with the pathology of bronchial asthma. If he reads the literature of the autopsy reports, he will find there are two types of asthma, the allergic and the so-called bronchitic which may simulate allergic asthma. The bronchial mucous plugs are not present in the bronchitic type but are found in the allergic. If one sees the autopsy material of a patient dying during a paroxysm, one is impressed with the solid plugs filling the greater part of the bronchial tree. We cannot merely dismiss this as an incidental finding.

Protocols of cases of true allergic asthma found in the literature consistently describe bronchial mucous plugging. I cannot see how we can deny or close our eyes to this finding and readily accept other factors which cannot be demonstrated or are merely inferential.

I wish I could take time to answer the question regarding the relation of guinea pig anaphylaxis and human asthmatic attack. I admit it is one of the most stimulating conceptions of the last twenty-five years, in regard to allergy, just as stimulating as the side chain theory of Ehrlich was to immunology, but it is becoming a ball and chain to our imagination.

Histamine: The Reactive Substance in Human Dander. JOHN A. MURPHY AND HERBERT M. COBE, PHILADELPHIA. (For original article, see page 161.)

DISCUSSION

DR. GEORGE PINESS, LOS ANGELES.—I should like to ask Dr. Murphy for a comparative description of the reactions that occurred with the histamine product as compared with the dander test.

DR. COBE.—I should like to answer Dr. Piness' question. The character of the reaction, is a wheal, of course depending on the size of the reaction, a slightly raised wheal. We used 2.5 cm. as a standard, in the erythema with histamine it is much larger than with any of the other proteins, but using that in a dilution of 1 to 10,000 as an arbitrary standard, we were able to evaluate other readings from that point.

Errata

In the abstract of Dr. Alexander Sterling's article, "Intradermal Bacterial Suspensions and House Dust Extract in Respiratory Disease," November issue, page 89, third line from the bottom of the page should read: 2,000,000 organisms per c.c., etc.

On page 90, third line from the bottom of the abstract, should read: lergens (2,000,000 organisms per c.c.) and for house dust, etc.

Department of Reviews and Abstracts

Selected Abstracts

Enuresis of Allergic Origin. Bray, G. W. Arch. Dis. Child. 6: 251, 1931.

The author states that within his experience some cases of persistent enuresis in children were allergic in origin. Such cases he classifies into three categories: (1) Cases in which enuresis occurs along with such allergic manifestations as asthma, hay fever, urticaria, etc. Three case reports are given in illustration in which the symptoms disappeared following the removal of the offending allergen. (2) Cases in which enuresis occurs along with conditions proved to be allergic in origin. A case report is given. (3) Cases in which enuresis occurs as the only manifestation of allergy.

The author investigated cases in the clinic of The Hospital for Sick Children, Great Ormond Street, London. Among the children under observation were those who had been treated for enuresis without success over a period of years with dietary and fluid restrictions and large doses of belladonna. No urinary abnormalities could be detected. Three cases out of 15 responded to the elimination of substances giving positive skin reactions. Analogy between enuresis and allergic conditions may be traced in the similarity in innervation of the bladder and the lungs. Stimulation of the parasympathetic system may lead to bronchospasm, or to the discharge of urine or to both according to the location or the intensity of the stimulus. In cases of persistent enuresis which fail to respond to the usual routine treatment, it is suggested that skin tests may point to an offending protein. With the elimination of contact with this protein, the symptoms may subside.

Allergic Manifestation to Insulin. Grishaw, W. H. J. A. M. A. 97: 1885, 1931.

The author reports the case of a man of thirty-eight years, with a family history of asthma, and a past history of urticaria and angioneurotic edema. When first seen, the patient was suffering from diabetes and pulmonary tuberculosis. Insulin injections were begun, and with each injection there appeared a reaction of the skin with redress, swelling and itching localized to the site of administration. This reaction occurred constantly for twenty-five days. At this time, a generalized urticarial eruption developed fifteen minutes after the morning dose. The evening dose was given from a different bottle of the same manufacture (A) and a similar reaction occurred. In addition there was swelling of the hands, lips and eyelids. Then an injection of insulin from a different laboratory (B) was given, with similar results. Finally, insulin from still another source (C) was injected without reaction, and this insulin has been tolerated since. Intradermal tests with the three samples were done. Positive results were obtained with A and B, but not with C. It is noteworthy that A was derived from pork and beef, B from beef and C from beef. Skin tests to pork, beef and veal were negative. On adding acetone to the various specimens, a precipitate formed. After filtration the acetone was driven off, and skin reactions with the acetone-free filtrates were done. Reactions were negative.

An attempt at passive transfer, by injecting the patient's serum into normal skin and then insulin at the same site failed to elicit a reaction. The inference is drawn that the patient is not sensitive to insulin but to some undetermined product in particular preparations of insulin.

A Pollen Survey of Miami, Florida. Nichol, E. S., and Durham, O. C. Southern M. J. **24**: 947, 1931.

This survey covers a two-year period and was undertaken because no facts heretofore were available on plants growing in this vicinity that caused hay fever. It is noteworthy that the pollen counts, on the whole, were very low. The reason for this is attributed to the character of the land and the lack of extensive agricultural areas. Moreover, during the summer and fall, the prevailing winds are from the ocean.

The most important grasses are Bermuda and natal grass, and these may be found pollinating all the year with the exception of January and a part of February. Johnson grass is next in importance and the season for it is nearly as extensive. Indian grass and broom sedge are definitely limited to the fall months. No giant ragweed is found in Florida. Short ragweed begins to bloom in the latter part of May and persists until October. Although there is very little within the environs of Miami, it is fairly abundant in the glades nearby, where it grows to an enormous height. Despite this profuse growth, very little ragweed pollen appeared on the slides, far less than in any of the Eastern and Middle Western cities. This is partially explained by the theory that ragweeds in Florida spend their efforts more in the vegetation process than in reproduction. The authors state that the seacoast of Florida is just about as nearly perfect for ragweed hay fever sufferers as a place could be. Tree pollens seem to play a very small rôle.

An Evaluation of the Skin Test in Allergy. Alexander, H. L. Ann. Int. Med. **5**: 52, 1931.

A review of a series of positive skin reactions reported by various observers, shows great individual discrepancies. These are attributed to a lack of standardization of each of the elements that enter into the test. To arrive at some understanding as to the value of the skin test, a large series of reported cases was compiled. This comprised 11,443 cases of allergy reported by 44 observers. It was found that positive skin reactions occurred in the allergic manifestations studied, as follows: hay fever 93.2 per cent, vasomotor rhinitis 55.7 per cent, eczema (infant and adult) 52.7 per cent, bronchial asthma 52.7 per cent, gastrointestinal allergy, 26.5 per cent.

The incidence of reactions with common allergens (excluding pollens) was then compiled. The reports of 32,182 tests were examined. Of the inhalant group feathers gave 20.3 per cent positive reactions, or about one positive for every five tests done with feathers. In order named, then, orris root 16.9 per cent, horse dander 16.6 per cent, wool 11.3 per cent, pyrethrum 9.3 per cent, cat dander 9.2 per cent, cattle dander 8.7 per cent, dog dander 8.3 per cent. All other inhalants gave less than 5 per cent. Of the foods in order, wheat gave 22.4 per cent, egg 18.4 per cent, milk 14.8 per cent, chocolate 13.9 per cent, spinach 13.3 per cent, beans 12.9 per cent, potato 12.1 per cent, tomato 11.9 per cent, carrot 11.8 per cent, pea 11.5 per cent, barley 10.7 per cent, rye 8.9 per cent, pork 8.3 per cent, beef 7.7 per cent, oats 6.7 per cent, corn 5.7 per cent, rice 5.7 per cent, all others less than 5 per cent. It is noteworthy that the figures for spinach, tomato, carrot, pea, barley, oat and rice appeared mostly in cases of infantile eczema. Pepper gave 17.5 per cent, but notations were made frequently that this may be a nonspecific reaction.

The inference is drawn that if one tests with this list of allergens as well as with pollens one will secure a positive reaction in a high percentage of cases of allergy which are capable of responding with positive reactions.

Is Psoriasis an Allergic Disease? Zeidler, R. Wien. med. Wchnschr. **81**: 877, 1931.

In a series of patients treated with pollen extracts for hay fever there were several individuals who suffered also with psoriasis vulgaris. It came to the attention of the writer, that in the course of treatments with pollen extract injection, the psoriasis was likewise relieved. The question arose as to whether this was simply a spontaneous remission or an effect attributable to the pollen therapy.

Experiments were performed to discover: (1) How a normal skin (no symptoms of hay fever) reacted to tests with pollen extracts. (2) How a psoriasitic skin (no symptoms of hay fever) reacted.

Results showed that no normal skin gave a positive reaction to the pollen extracts. From patients with psoriasis vulgaris, however, a positive reaction to the pollen extracts was elicited. It was observed that the course of the psoriasis vulgaris ran parallel with the skin reaction. When a cutaneous reaction with the strongest concentration of pollen extract could no longer be elicited, the psoriasis also diminished to a point where it was practically cured. It was found, further, that 22 per cent of patients with psoriasis showed some nasal symptoms typical of hay fever or rhinitis conditions.

The etiology of psoriasis vulgaris has long been a matter of much dispute. The findings of the present writer bring up the possibility of an allergic etiology. Whether the psoriasis is an allergic reaction to the excitant of hay fever and therefore only a symptom of hay fever, or a reaction by hypersensitive individuals to various specific foreign substances, the writer is not prepared to state at the present time.

Passive Anaphylaxis. Injections Into Rabbits of Human Serum from Hypersensitive Individuals, Mixed With the Specific Allergen. Vallery-Radot, P., Maubic, G., Hugo, A., and Giroud, P. Compt. rend. Soc. de biol. **107**: 707, 1931.

Having failed to accomplish passive transfer of anaphylaxis by injecting human serum from hypersensitive individuals into rabbits and at some time thereafter injecting the specific allergen, the authors undertook to mix the serum and allergen in vitro. Patients giving positive Prausnitz-Küstner reactions and those with positive skin reactions were chosen. Fifteen experiments were done. In eight, the serum and allergen were allowed to stand at room temperature for one-half hour; in one, two hours; and in six, twenty-four hours. In some, the mixtures were centrifuged and the supernatant fluid was injected; in others the whole mixtures were administered. In no instance was passive anaphylaxis obtained. In 10 control experiments with normal serum and allergens, no anaphylaxis was obtained. Consequently, passive transfer of anaphylaxis could not be accomplished by mixtures of reagins and allergens.

Book Reviews

RECENT ADVANCES IN ALLERGY (ASTHMA, HAY FEVER, ECZEMA, MIGRAINE, ETC.). George W. Bray, M.B., Ch.M., with a foreword by Arthur F. Hurst, M.D., F.R.C.P. Cloth. Pp. 432, illustrated. P. Blackiston's Son & Co., Philadelphia.

In the preface of this book, the author states that his aim in writing it has been to provide in a handy and inexpensive form, a *résumé* of our present state of knowledge and the trend of modern research in allergy in general and its individual manifestations in particular. The author, a leading authority on allergy, has been singularly successful in accomplishing his purpose. The particular value of this book is the concise way in which each of the many aspects of allergy is summed up. At the same time there is a large supporting bibliography so that the reader is well supplied with original sources should he wish to enlarge his knowledge on any particular point.

Of significance to those interested in the botanical aspect of plants that cause hay fever, is a chapter in which plants in the British Isles are classified and illustrated. This is probably the first such compilation in the medical literature.

The subject of allergy is growing so extensively that it is most difficult for any but the specialist to keep abreast of it. This book, with its emphasis on clinical research, admirably serves that purpose, as well as that of a valuable work of reference.